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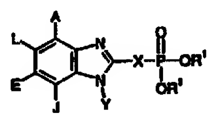
(54) Title: NOVEL BENZIMIDAZOLE INHIBITORS OF FRUCTOSE–1,6–BISPHOSPHATASE

(57) Abstract



(1)

Novel benzimidazole compounds of structure (1) and their use as fructose–1,6–bisphosphatase inhibitors is described wherein A, E, and L are selected from the group consisting of $-NR^8{}_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, –CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloakolxy, C1–C5 alkyl, C2–C5 alkenyl, C2–C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic; J is selected from the group consisting $-NR^8{}_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-C(O)R^{11}$, –CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl; X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1–dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic; Y is selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2{}_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic; and pharmaceutically acceptable prodrugs and salts thereof.

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NOVEL BENZIMIDAZOLE INHIBITORS OF FRUCTOSE 1,6-BISPHOSPHATASE

Field of the Invention

This invention relates to novel benzimidazole compounds that are inhibitors of Fructose-1,6-bisphosphatase at the AMP site. The invention also relates to the preparation and use of these benzimidazole analogs in the treatment of diabetes, and other diseases where the inhibition of gluconeogenesis, control of blood glucose levels, reduction in glycogen stores, or reduction in insulin levels is beneficial.

Background and Introduction to the Invention

Diabetes mellitus (or diabetes) is one of the most prevalent diseases in the world today. Diabetes patients have been divided into two classes, namely type I or insulin-dependent diabetes mellitus and type II or non-insulin dependent diabetes mellitus (NIDDM). Non-insulin-dependent diabetes mellitus (NIDDM) accounts for approximately 90% of all diabetics and is estimated to affect 12-14 million adults in the U. S. alone (6.6% of the population). NIDDM is characterized by both fasting hyperglycemia and exaggerated postprandial increases in plasma glucose levels. NIDDM is associated with a variety of long-term complications, including microvascular diseases such as retinopathy, nephropathy and neuropathy, and macrovascular diseases such as coronary heart disease. Numerous studies in animal models demonstrate a causal relationship between long term complications and hyperglycemia. Recent results from the Diabetes Control and Complications Trial (DCCT) and the Stockholm Prospective Study demonstrate this relationship for the first time in man by showing that insulin-dependent diabetics with tighter glycemic control are at substantially lower risk for development and progression of these complications. Tighter control is also expected to benefit NIDDM patients.

Current therapies used to treat NIDDM patients entail both controlling lifestyle risk factors and pharmaceutical intervention. First-line therapy for NIDDM is typically a tightly-controlled regimen of diet and exercise since an overwhelming number of NIDDM patients are overweight or obese (≈ 67%) and since weight loss can improve insulin secretion, insulin sensitivity and lead to normoglycemia. Normalization of blood glucose occurs in less than 30% of these patients due to poor compliance and poor response. Patients with

hyperglycemia not controlled by diet alone are subsequently treated with oral hypoglycemics or insulin. Until recently, the sulfonylureas were the only class of oral hypoglycemic agents available for NIDDM. Treatment with sulfonylureas leads to effective blood glucose lowering in only 70% of patients and only 40% after 10 years of therapy. Patients that fail to respond to diet and sulfonylureas are subsequently treated with daily insulin injections to gain adequate glycemic control.

Although the sulfonylureas represent a major therapy for NIDDM patients, four factors limit their overall success. First, as mentioned above, a large segment of the NIDDM population do not respond adequately to sulfonylurea therapy (*i.e.* primary failures) or become resistant (*i.e.* secondary failures). This is particularly true in NIDDM patients with advanced NIDDM since these patients have severely impaired insulin secretion. Second, sulfonylurea therapy is associated with an increased risk of severe hypoglycemic episodes. Third, chronic hyperinsulinemia has been associated with increased cardiovascular disease although this relationship is considered controversial and unproven. Last, sulfonylureas are associated with weight gain, which leads to worsening of peripheral insulin sensitivity and thereby can accelerate the progression of the disease.

Recent results from the U.K. Diabetes prospective study also showed that patients undergoing maximal therapy of a sulfonylurea, metformin, or a combination of the two, were unable to maintain normal fasting glycemia over the six year period of the study. U.K. Prospective Diabetes Study 16. Diabetes, 44:1249-158 (1995). These results further illustrate the great need for alternative therapies. Three therapeutic strategies that could provide additional health benefits to NIDDM patients beyond the currently available therapies, include drugs that would: (i) prevent the onset of NIDDM; (ii) prevent diabetic complications by blocking detrimental events precipitated by chronic hyperglycemia; or (iii) normalize glucose levels or at least decrease glucose levels below the threshold reported for microvascular and macrovascular diseases.

Hyperglycemia in NIDDM is associated with two biochemical abnormalities, namely insulin resistance and impaired insulin secretion. The relative roles of these metabolic abnormalities in the pathogenesis of NIDDM has been the subject of numerous studies over the past several decades. Studies of offspring and siblings of NIDDM patients, mono- and dizygotic twins,

and ethnic populations with high incidence of NIDDM (*e.g.* Pima Indians) strongly support the inheritable nature of the disease.

Despite the presence of insulin resistance and impaired insulin secretion, fasting blood glucose (FBG) levels remain normal in pre-diabetic patients due to a state of compensatory hyperinsulinemia. Eventually, however, insulin secretion is inadequate and fasting hyperglycemia ensues. With time insulin levels decline. Progression of the disease is characterized by increasing FBG levels and declining insulin levels.

Numerous clinical studies have attempted to define the primary defect that accounts for the progressive increase in FBG. Results from these studies indicate that excessive hepatic glucose output (HGO) is the primary reason for the elevation in FBG with a significant correlation found for HGO and FBG once FBG exceeds 140 mg/dL. Kolterman, et al., J. Clin. Invest. 68:957, (1981); DeFronzo Diabetes 37:667 (1988).

HGO comprises glucose derived from breakdown of hepatic glycogen (glycogenolysis) and glucose synthesized from 3-carbon precursors (gluconeogenesis). A number of radioisotope studies and several studies using ^{13}C-NMR spectroscopy have shown that gluconeogenesis contributes between 50-100% of the glucose produced by the liver in the postabsorptive state and that gluconeogenesis flux is excessive (2- to 3-fold) in NIDDM patients. Magnusson, et al. J. Clin. Invest. 90:1323-1327 (1992); Rothman, et al., Science 254: 573-76 (1991); Consoli, et a l. Diabetes 38:550-557 (1989).

Gluconeogenesis from pyruvate is a highly regulated biosynthetic pathway requiring eleven enzymes (Figure 1). Seven enzymes catalyze reversible reactions and are common to both gluconeogenesis and glycolysis. Four enzymes catalyze reactions unique to gluconeogenesis, namely pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase. Overall flux through the pathway is controlled by the specific activities of these enzymes, the enzymes that catalyzed the corresponding steps in the glycolytic direction, and by substrate availability. Dietary factors (glucose, fat) and hormones (insulin, glucagon, glucocorticoids, epinephrine) coordinatively regulate enzyme activities in the gluconeogenesis and glycolysis pathways through gene expression and post-translational mechanisms.

Of the four enzymes specific to gluconeogenesis, fructose-1,6-bisphosphatase (hereinafter "FBPase") is the most suitable target for a gluconeogenesis inhibitor based on efficacy and safety considerations. Studies indicate that nature uses the FBPase/PFK cycle as a major control point (metabolic switch) responsible for determining whether metabolic flux proceeds in the direction of glycolysis or gluconeogenesis. Claus, et al., Mechanisms of Insulin Action, Belfrage, P. editor, pp.305-321, Elsevier Science 1992; Regen, et al. J. Theor. Biol., 111:635-658 (1984); Pilkis, et al. Annu. Rev. Biochem, 57:755-783 (1988). FBPase is inhibited by fructose-2,6-bisphosphate in the cell. Fructose-2,6-bisphosphate binds to the substrate site of the enzyme. AMP binds to an allosteric site on the enzyme.

Synthetic inhibitors of FBPase have also been reported. McNiel reported that fructose-2,6-bisphosphate analogs inhibit FBPase by binding to the substrate site. J. Med. Chem., 106:7851 (1984); U.S. Patent No. 4,968,790 (1984). These compounds, however, were relatively weak and did not inhibit glucose production in hepatocytes presumably due to poor cell penetration.

Gruber reported that some nucleosides can lower blood glucose in the whole animal through inhibition of FBPase. These compounds exert their activity by first undergoing phosphorylation to the corresponding monophosphate. EP 0 427 799 B1.

Gruber et al. U.S. Patent No. 5,658,889 described the use of inhibitors of the AMP site of FBPase to treat diabetes.

J. Med. Chem. 32:1528-32 (1989) discloses lower alkyl phosphonic esters of benzimidazole compounds where X in formula 1 of the present invention is -pyridyl-CH_2-. This publication discusses Ca^{2+} antagonist activity. There is no suggestion that the disclosed compounds were FBPase inhibitors or that they have blood glucose lowering activity. Furthermore, lower alkyl phosphonic esters are not FBPase inhibitors and are not readily hydrolyzed into active compounds within the body.

European patent application EP 0 620 227 A1 discloses certain heterocycles including benzimidazoles having a diphosphonic acid where the X linker in formula 1 of the claims is alkylamino and alkylaminoalkyl. These compounds are said to inhibit bone resorption. There is no suggestion that the disclosed compounds were FBPase inhibitors or that they have blood glucose lowering activity.

German Offenlegungsschrift 2855659 discloses certain free phosphonic acids of benzimidazoles where A is amino and X is alkyl or alkene. These compounds are supposed to be corrosion inhibitors. There is no suggestion that the disclosed compounds were FBPase inhibitors or that they have blood glucose lowering activity.

Brief Description of the Drawings

FIG. 1 is a scheme depicting the eleven enzymes of the gluconeogenesis pathway.

FIG. 2 shows that compounds **12.61**, **12.53**, **12.52**, and **12.64** inhibit human liver FBPase activity *in vitro* in a dose dependent manner.

FIG. 3 shows that compound **12.1** and ZMP displaced AMP from human liver FBPase in a dose dependent manner.

FIG. 4 shows that compounds **12.1**, **12.53**, and **12.61** inhibit glucose production *in vitro* in rat hepatocytes.

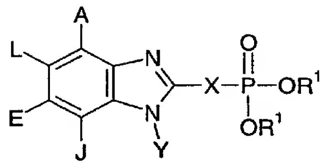
FIG. 5 shows the inhibition of glucose production and the accumulation of fructose-1,6-bisphosphate is dependent on the dose of compound **12.64**.

Summary of the Invention

The present invention is directed towards novel benzimidazole compounds which bind to the AMP site and are potent FBPase inhibitors. In another aspect, the present invention is directed to the preparation of these novel benzimidazole compounds and to the in vitro and in vivo FBPase inhibitory activity of these compounds. Another aspect of the present invention is directed to the clinical use of the novel FBPase inhibitors as a method of treatment or prevention of diseases responsive to inhibition of gluconeogenesis and in diseases responsive to lowered blood glucose levels.

The compounds are also useful in treating or preventing excess glycogen storage diseases and insulin dependent diseases such as cardiovascular diseases including atherosclerosis.

The invention comprises the novel benzimidazole analogs as specified below in formula 1. Also included in the scope of the present invention are prodrugs of the compounds of formula 1.



Formula 1

Since these compounds may have asymmetric centers, the present invention is directed not only to racemic mixtures of these compounds, but also to individual stereoisomers. The present invention also includes pharmaceutically acceptable and/or useful salts of the compounds of formula 1, including acid addition salts. The present inventions also encompass prodrugs of compounds of formula 1.

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted.

Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups and polycyclic or fused compounds such as optionally substituted naphthyl groups.

Heterocyclic aryl groups are groups having from 1 to 4 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Suitable heteroaryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, and the like, all optionally substituted.

The term "biaryl" represents aryl groups containing more than one aromatic ring including both fused ring systems and aryl groups substituted with other aryl groups.

The term "alicyclic" means compounds which combine the properties of aliphatic and cyclic compounds and include but are not limited to aromatic, cycloalkyl and bridged cycloalkyl compounds. The cyclic compound includes heterocycles. Cyclohexenylethyl, cyclohexanylethyl, and norbornyl are suitable alicyclic groups. Such groups may be optionally substituted.

The term "optionally substituted" or "substituted" includes groups substituted by one to four substituents, independently selected from lower alkyl, lower aryl, lower aralkyl, lower alicyclic, hydroxy, lower alkoxy, lower aryloxy, perhaloalkoxy, aralkoxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroaralkoxy, azido, amino, guanidino, halogen, lower alkylthio, oxa, ketone, carboxy esters, carboxyl, carboxamido, nitro, acyloxy, alkylamino, aminoalkyl, alkylaminoaryl, alkylaryl, alkylaminoalkyl, alkoxyaryl, arylamino, aralkylamino, phosphonate, sulfonate, carboxamidoalkylaryl, carboxamidoaryl, hydroxyalkyl, haloalkyl, alkylaminoalkylcarboxy, aminocarboxamidoalkyl, cyano, lower alkoxyalkyl, and lower perhaloalkyl.

The term "aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include benzyl, picolyl, and the like, and may be optionally substituted.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such as with up to and including 10, preferably up to and including 6, and advantageously one to four carbon atoms. Such groups may be straight chain, branched, or cyclic.

The terms "arylamino" (a), and "aralkylamino" (b), respectively, refer to the group -NRR' wherein respectively, (a) R is aryl and R' is hydrogen, alkyl, aralkyl or aryl, and (b) R is aralkyl and R' is hydrogen or aralkyl, aryl, alkyl.

The term "acyl" refers to -C(O)R where R is alkyl and aryl.

The term "carboxy esters" refers to -C(O)OR where R is alkyl, aryl, aralkyl, and alicyclic, all optionally substituted.

The term "oxa" refers to =O in an alkyl group.

The term "alkylamino" refers to -NRR' where R and R' are independently selected from hydrogen or alkyl.

The term "carbonylamine" or "carbonylamino" refers to $-CONR_2$ where each R is independently hydrogen or alkyl.

The term "halogen" or "halo" refers to -F, -Cl, -Br and -I.

The term "oxyalkylamino" refers to -O-alk-NR-, where "alk" is an alkylene group and R is H or alkyl.

The term “alkylsulfonate” refers to the group -alk-$S(O)_2$-O- where “alk” is an alkylene group.

The term “alkylaminoalkylcarboxy” refers to the group -alk-NR-alk-C(O)-O- where “alk” is an alkylene group, and R is a H or lower alkyl.

The term “alkylaminocarbonyl” refers to the group -alk-NR-C(O)- where “alk” is an alkylene group, and R is a H or lower alkyl.

The term “oxyalkyl” refers to the group -O-alk- where “alk” is an alkylene group.

The term “alkylcarboxyalkyl” refers to the group -alk-C(O)-O-alkyl where each alk is independently an alkylene group.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched chain and cyclic groups. Alkyl groups may be optionally substituted.

The term “bidentate” refers to an alkyl group that is attached by its terminal ends to the same atom to form a cyclic group. For example, propylene imine contains a bidentate propylene group.

The term “cyclic alkyl” refers to alkyl groups that are cyclic.

The term “heterocyclic” and “heterocyclic alkyl” refer to cyclic alkyl groups containing at least one heteroatom. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Heterocyclic groups may be attached through a heteroatom or through a carbon atom in the ring.

The term "alkenyl" refers to unsaturated groups which contain at least one carbon-carbon double bond and includes straight-chain, branched-chain and cyclic groups. Alkene groups may be optionally substituted.

The term "alkynyl" refers to unsaturated groups which contain at least one carbon-carbon triple bond and includes straight-chain, branched-chain and cyclic groups. Alkyne groups may be optionally substituted.

The term "alkylene" refers to a divalent straight chain, branched chain or cyclic saturated aliphatic radical.

The term “acyloxy” refers to the ester group -O-C(O)R, where R is H, alkyl, alkenyl, alkynyl, aryl, aralkyl, or alicyclic.

The term “alkylaryl” refers to the group -alk-aryl- where “alk” is an alkylene group. “Lower alkylaryl” refers to such groups where alkylene is lower alkyl.

The term “alkylamino” refers to the group -alk-NR- wherein “alk” is an alkylene group.

The term “alkyl(carboxyl)” refers to carboxyl substituted off the alkyl chain. Similarly, “alkyl(hydroxy)”, “alkyl(phosphonate)”, and “alkyl(sulfonate)” refers to substituents off the alkyl chain.

The term “alkylaminoalkyl” refers to the group -alk-NR-alk- wherein each “alk” is an independently selected alkylene, and R is H or lower alkyl. “Lower alkylaminoalkyl” refers to groups where each alkylene group is lower alkyl.

The term “alkylaminoaryl” refers to the group -alk-NR-aryl- wherein “alk” is an alkylene group. In “lower alkylaminoaryl”, the alkylene group is lower alkyl.

The term “alkyloxyaryl” refers to an alkylene group substituted with an aryloxy group. In “lower alkyloxyaryl”, the alkylene group is lower alkyl.

The term “alkylacylamino” refers to the group -alk-N-(COR)- wherein alk is alkylene and R is lower alkyl. In “lower alkylacylamino”, the alkylene group is lower alkyl.

The term “alkoxyalkylaryl” refers to the group -alk-O-alk-aryl- wherein each “alk” is independently an alkylene group. “Lower aloxyalkylaryl” refers to such groups where the alkylene group is lower alkyl.

The term “alkylacylaminoalkyl refers to the group -alk-N-(COR)-alk- where each alk is an independently selected alkylene group. In “lower alkylacylaminoalkyl” the alkylene groups are lower alkyl.

The term “alkoxy” refers to the group -alk-O- wherein alk is an alkylene group.

The term “alkoxyalkyl” refers to the group -alk-O-alk- wherein each alk is an independently selected alkylene group. In “lower alkoxyalkyl”, each alkylene is lower alkyl.

The term “alkylthio” refers to the group -alk-S- wherein alk is alkylene group.

The term “alkylthioalkyl” refers to the group -alk-S-alk- wherein each alk is an independently selected alkylene group. In “lower alkylthioalkyl” each alkylene is lower alkylene.

The term “aralkylamino” refers to an amine substituted with an aralkyl group.

The term “alkylcarboxamido” refers to the group -alk- C(O)N(R)- wherein alk is an alkylene group and R is H or lower alkyl.

The term "alkylcarboxamidoalkyl" refers to the group -alk-C(O)N(R)-alk- wherein each alk is an independently selected alkylene group and R is lower alkyl. In "lower alkylcarboxamidoalkyl" each alkylene is lower alkyl.

The term "alkylcarboxamidoalkylaryl" refers to the group -alk_1-C(O)-NH-alk_2Ar- wherein alk_1 and alk_2 are independently selected alkylene groups and alk_2 is substituted with an aryl group, Ar. In "lower alkylcarboxamidoalkylaryl", each alkylene is lower alkyl.

The term "heteroalicyclic" refers to an alicyclic group having 1 to 4 heteroatoms selected from nitrogen, sulfur, phosphorus and oxygen.

The term "aminocarboxamidoalkyl" refers to the group -NH-C(O)-N(R)-R wherein each R is an independently selected alkyl group. "Lower aminocaboxamidoalkyl" refers to such groups wherein each R is lower alkyl.

The term "heteroarylalkyl" refers to an alkyl group substituted with a heteroaryl group.

The term "perhalo" refers to groups wherein every C-H bond has been replaced with a C-halo bond on an aliphatic or aryl group. Suitable perhaloalkyl groups include -CF_3 and -$CFCl_2$.

The term "guanidine" refers to both -NR-C(NR)-NR_2 as well as -N=C(NR_2)$_2$ where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

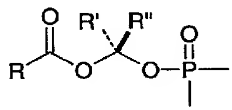
The term "amidine" refers to -C(NR)-NR_2 where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

The term "pharmaceutically acceptable salt" includes salts of compounds of formula 1 and its prodrugs derived from the combination of a compound of this invention and an organic or inorganic acid or base.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the "drug" substance either as a result of spontaneous chemical reaction(s) or by enzyme catalyzed or metabolic reaction(s). Reference is made to various prodrugs such as acyl esters, carbonates, and carbamates, included herein. The groups illustrated are exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula 1, fall within the scope of the present invention.

The term "prodrug ester" as employed herein includes, but is not limited to, the following groups and combinations of these groups:

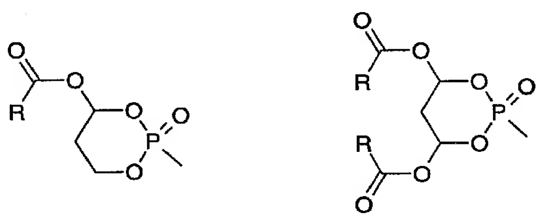
[1] Acyloxyalkyl esters which are well described in the literature (Farquhar et al., J. Pharm. Sci. 72, 324-325 (1983)) and are represented by formula A



Formula A

wherein R, R', and R" are independently H, alkyl, aryl, alkylaryl, and alicyclic; (see WO 90/08155; WO 90/10636).

[2] Other acyloxyalkyl esters are possible in which an alicyclic ring is formed such as shown in formula B. These esters have been shown to generate phosphorus-containing nucleotides inside cells through a postulated sequence of reactions beginning with deesterification and followed by a series of elimination reactions (e.g. Freed et al., Biochem. Pharm. 38: 3193-3198 (1989)).

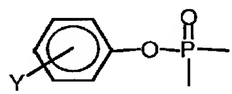


Formula B

wherein R is -H, alkyl, aryl, alkylaryl, alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, cycloalkyl, or alicyclic.

[3] Another class of these double esters known as alkyloxycarbonyloxymethyl esters, as shown in formula A, where R is alkoxy, aryloxy, alkylthio, arylthio, alkylamino, and arylamino; R', and R" are independently H, alkyl, aryl, alkylaryl, and alicyclic, have been studied in the area of β-lactam antibiotics (Tatsuo Nishimura et al. *J. Antibiotics*, **1987**, *40(1)*, 81-90; for a review see Ferres, H., *Drugs of Today*, **1983**, *19*, 499.). More recently Cathy, M. S., et al. (Abstract from AAPS Western Regional Meeting, April, **1997**) showed that these alkyloxycarbonyloxymethyl ester prodrugs on (9-[(R)-2-phosphonomethoxy)propyl]adenine (PMPA) are bioavailable up to 30% in dogs.

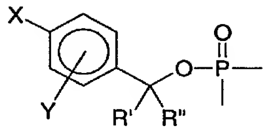
[4] Aryl esters have also been used as phosphonate prodrugs (*e.g.* Erion, DeLambert et al., J. Med. Chem. 37: 498, 1994; Serafinowska et al., J. Med. Chem. 38: 1372, 1995). Phenyl as well as mono and poly-substituted phenyl proesters have generated the parent phosphonic acid in studies conducted in animals and in man (Formula C). Another approach has been described where Y is a carboxylic ester ortho to the phosphate. Khamnei and Torrence, J. Med. Chem.; 39:4109-4115 (1996).



Formula C

wherein Y is H, alkyl, aryl, alkylaryl, alkoxy, acetoxy, halogen, amino, alkoxycarbonyl, hydroxy, cyano, alkylamino, and alicyclic.

[5] Benzyl esters have also been reported to generate the parent phosphonic acid. In some cases, using substituents at the para-position can accelerate the hydrolysis. Benzyl analogs with 4-acyloxy or 4-alkyloxy group [Formula D, X = H, OR or O(CO)R or O(CO)OR] can generate the 4-hydroxy compound more readily through the action of enzymes, *e.g.* oxidases, esterases, etc. Examples of this class of prodrugs are described in Mitchell et al., J. Chem. Soc. Perkin Trans. I 2345 (1992); Brook, et al. WO 91/19721.

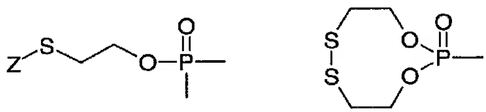


Formula D

wherein X and Y are independently H, alkyl, aryl, alkylaryl, alkoxy, acetoxy, hydroxy, cyano, nitro, perhaloalkyl, halo, or alkyloxycarbonyl; and

R' and R" are independently H, alkyl, aryl, alkylaryl, halogen, and alicyclic.

[6] Thio-containing phosphonate proesters have been described that are useful in the delivery of FBPase inhibitors to hepatocytes. These proesters contain a protected thioethyl moiety as shown in formula E. One or more of the oxygens of the phosphonate can be esterified. Since the mechanism that results in de-esterification requires the generation of a free thiolate, a variety of thiol protecting groups are possible. For example, the disulfide is reduced by a reductase-mediated process (Puech et al., Antiviral Res., 22: 155-174 (1993)). Thioesters will also generate free thiolates after esterase-mediated hydrolysis. Benzaria, et al., J. Med. Chem., 39:4958 (1996). Cyclic analogs are also possible and were shown to liberate phosphonate in isolated rat hepatocytes. The cyclic disulfide shown below has not been previously described and is novel.

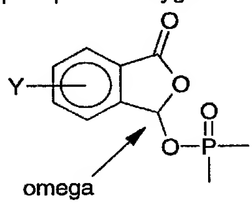


Formula E

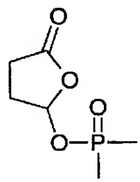
wherein Z is alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, or alkylthio.

Other examples of suitable prodrugs include proester classes exemplified by Biller and Magnin (U.S. Patent No. 5,157,027); Serafinowska et al. (J. Med. Chem. 38, 1372 (1995)); Starrett et al. (J. Med. Chem. 37, 1857

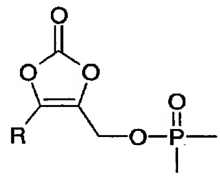
(1994)); Martin et al. J. Pharm. Sci. 76, 180 (1987); Alexander et al., Collect. Czech. Chem. Commun, 59, 1853 (1994)); and EPO patent application 0 632 048 A1. Some of the structural classes described are optionally substituted, including fused lactones attached at the omega position and optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen such as:



3-phthalidyl



2-oxotetrahydrofuran-5-yl

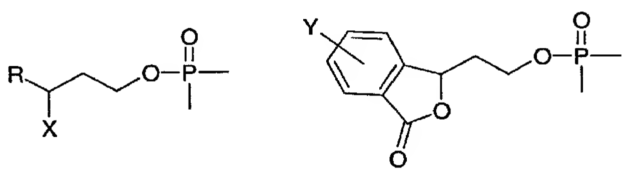


2-oxo-4,5-didehydro-1,3-dioxolanemethyl

wherein R is -H, alkyl, cycloalkyl, or alicyclic; and

wherein Y is -H, alkyl, aryl, alkylaryl, cyano, alkoxy, acetoxy, halogen, amino, alkylamino, alicyclic, and alkoxycarbonyl.

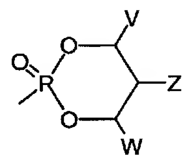
[7] Propyl phosphonate proesters can also be used to deliver FBPase inhibitors into hepatocytes. These proesters may contain a hydroxyl and hydroxyl group derivatives at the 3-position of the propyl group as shown in formula F. The R and X groups can form a cyclic ring system as shown in formula F. One or more of the oxygens of the phosphonate can be esterified.



Formula F

wherein R is alkyl, aryl, heteroaryl;
X is hydrogen, alkylcarbonyloxy, alkyloxycarbonyloxy; and
Y is alkyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, halogen, hydrogen, hydroxy, acetoxy, amino.

[8] The cyclic propyl phosphonate esters as in Formula G are shown to activate to phosphonic acids. The activation of prodrug can be mechanistically explained by *in vivo* oxidation and elimination steps. These prodrugs inhibit glucose production in isolated rat hepatocytes and are also shown to deliver FBPase inhibitors to the liver following oral administration.



Formula G

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

[9] Phosphoramidate derivatives have been explored as potential phosphonate prodrugs (e.g. McGuigan et al., *Antiviral Res.* **1990,** *14*: 345; **1991**, *15* : 255. Serafinowska et al., *J. Med. Chem.*, **1995**, *38*, 1372). Most phosphoramidates are unstable under aqueous acidic conditions and are hydrolyzed to the corresponding phosphonic acids. Cyclic phosphoramidates have also been studied as phosphonate prodrugs because of their potential for greater stability compared to non cyclic phosphoramidates (e.g. Starrett et al., *J. Med. Chem.*, **1994**, *37*: 1857).

Other prodrugs are possible based on literature reports such as substituted ethyls for example, bis(trichloroethyl)esters as disclosed by McGuigan, et al. Bioorg Med. Chem. Lett., 3:1207-1210 (1993), and the phenyl and benzyl combined nucleotide esters reported by Meier, C. et al. Bioorg. Med. Chem. Lett., 7:99-104 (1997).

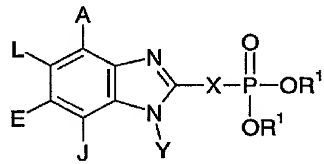
X group nomenclature as used herein in formula 1 describes the group attached to the phosphonate and ends with the group attached to the 2-position of the benzimidazole ring. For example, when X is alkylamino, the following structure is intended:

(benzimidazole ring)-NR-alk-P(O)$(OR^1)_2$

Y group nomenclature likewise ends with the group attached to the ring.

DETAILED DESCRIPTION OF THE INVENTION

Preferred compounds of the present invention are inhibitors of the AMP site of FBPase of the following formula 1:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

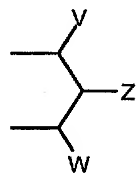
J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$,

$-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R^{10};

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, -NH_2, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, -NH_2 and -OR^3; and

pharmaceutically acceptable prodrugs and salts thereof; with the provisos that:

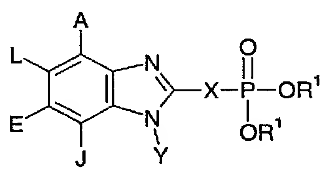
a) R^1 is not lower alkyl of 1-4 carbon atoms;

b) when X is alkyl or alkene, then A is -N(R^8_2);

c) X is not alkylamine and alkylaminoalkyl substituted with phosphonic esters and acids; and

d) A, L, E, J, Y, and X together may only form 0-2 cyclic groups.

Preferred compounds for the method of use claims are inhibitors of the AMP site of FBPase of the following formula 1:



wherein:

A, E, and L are selected from the group consisting of -NR^8_2, -NO_2, -H, -OR^7, -SR^7, -C(O)NR^4_2, halo, -COR^{11}, -SO_2R^3, guanidine, amidine, -NHSO_2R^5, -$SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl,

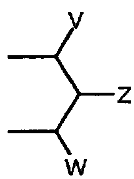
perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

Preferred Compounds of Formula 1

Suitable alkyl groups include groups having from 1 to about 20 carbon atoms. Suitable aryl groups include groups having from 1 to about 20 carbon atoms. Suitable aralkyl groups include groups having from 2 to about 21 carbon atoms. Suitable acyloxy groups include groups having from 1 to about 20 carbon atoms. Suitable alkylene groups include groups having from 1 to about 20 carbon atoms. Suitable alicyclic groups include groups having 3 to about 20 carbon atoms. Suitable heteroaryl groups include groups having from 1 to about 20 carbon atoms and from 1 to 5 heteroatoms, preferably independently selected from nitrogen, oxygen, phosphorous, and sulfur. Suitable heteroalicyclic groups include groups having from 2 to about twenty carbon atoms and from 1 to 5 heteroatoms, preferably independently selected from nitrogen, oxygen, phosphorous, and sulfur.

Preferred A, L, and E groups include -H, $-NR^8_2$, $-NO_2$, hydroxy, alkylaminocarbonyl, halogen, $-OR^7$, $-SR^7$, lower perhaloalkyl, and C1-C5 alkyl, or together E and J form a cyclic group. Such a cyclic group may be aromatic, cyclic alkyl, or heterocyclic alkyl, and may be optionally substituted. Suitable aromatic groups include thiazole. Particularly preferred A, L and E groups are $-NR^8_2$, -H, hydroxy, halogen, lower alkoxy, lower perhaloalkyl, and lower alkyl.

Preferred A groups include, $-NR^8_2$, -H, halogen, lower perhaloalkyl, and lower alkyl.

Preferred L and E groups include -H, lower alkoxy, lower alkyl, and halogen.

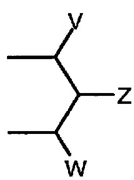
Preferred J groups include -H, halogen, lower alkyl, lower hydroxylalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower perhaloalkyl, lower alkenyl, lower alkynyl, lower aryl, heterocyclic, and alicyclic, or together with Y forms a cyclic group. Such a cyclic group may be aromatic, cyclic alkyl, or heterocyclic, and may be optionally substituted. Particularly preferred J groups include -H, halogen, and lower alkyl, lower hydroxyalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower alkenyl, alicyclic, and aryl. Especially preferred are alicyclic and lower alkyl.

Preferred X groups include alkyl, alkynyl, aryl, alkoxyalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, 1,1-dihaloalkyl, carbonylalkyl, alkyl(OH), and alkyl(sulfonate). Particularly preferred is heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, alkyl(sulfonate), and alkoxyalkyl. Also particularly preferred are heteroaryl, alkylaminocarbonyl, and alkoxyalkyl. Especially preferred are methylaminocarbonyl, methoxymethyl, and furanyl.

In one preferred aspect X is not substituted with a phosphonic acid or ester. In another preferred aspect, when X is substituted with a phosphonic acid or ester, then A is $-N(R^8)_2$ and Y is not -H. In another preferred aspect, when X is aryl or alkylaryl, these groups are not linked 1,4 through a 6-membered aromatic ring.

Preferred Y groups include -H, alkyl, aralkyl, aryl, and alicyclic, all except -H may be optionally substituted. Particularly preferred are lower alkyl, and alicyclic.

Preferred R^1 groups include -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted phenyl, optionally substituted benzyl, optionally substituted alkylaryl, $-C(R^2)_2OC(O)R^3$, $C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2$-OC(O)SR^3, -alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxyl, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are alkyl-S-S-alkyl to form a cyclic group, or R^1 and R^1 together are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,

alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

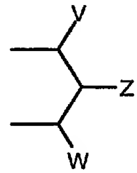
R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

Preferred such R^1 groups include optionally substituted phenyl, optionally substituted benzyl, -H, and $-C(R^2)_2OC(O)R^3$. Also preferred are such groups where at least one R^1 is aryl or-$C(R^2)_2$ aryl. Particularly preferred is H. Also preferred is when at least one R^1 is alkyl, preferably greater than 4 carbon atoms. Another preferred aspect is when at least one R^1 is $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-OC(O)OR^3$, $-C(R^2)_2-OC(O)SR^3$. Also particularly preferred is when R^1 and R^1 together are optionally substituted, including fused, lactones attached at the omega position or are optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen. Also preferred is when at least one R^1 is -alkyl-S-S-alkylhydroxyl, -alkyl-S-C(O)R^3, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group. Also preferred is

where R^1 and R^1 together are



to form a cyclic group,

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

Particularly preferred are such groups wherein V and W both form a 6-membered carbocyclic ring substituted with 0-4 groups, selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, and alkoxy; and Z is $-R^2$. Also particularly preferred are such groups wherein V and W are hydrogen; and Z is selected from the group consisting of hydroxyalkyl, acyloxyalkyl,

alkyloxyalkyl, and alkoxycarboxyalkyl. Also particularly preferred are such groups wherein V and W are independently selected from the group consisting of hydrogen, optionally substituted aryl, and optionally substituted heteroaryl, with the proviso that at least one of V and W is optionally substituted aryl or optionally substituted heteroaryl.

Also particularly preferred are such compounds where R^1 is alicyclic where the cyclic moiety contains carbonate or thiocarbonate.

Preferred R^4 and R^7 groups include -H, and lower alkyl.

In one preferred aspect A, L, and E are independently -H, lower alkyl, hydroxy, halogen, lower alkoxy, lower perhaloalkyl, and $-NR^8_2$; X is aryl, alkoxyalkyl, alkyl, alkylthio, 1,1-dihaloalkyl, carbonylalkyl, alkyl(hydroxy), alkyl(sulfonate), alkylaminocarbonyl, and alkylcarbonylamino; and each R^4 and R^7 is independently -H, and lower alkyl. Particularly preferred are such compounds where A, L, and E are independently -H, lower alkyl, halogen, and $-NR^8_2$; J is -H, halogen, haloalkyl, hydroxyalkyl, R^8_2N-alkyl, lower alkyl, lower aryl, heterocyclic, and alicyclic, or together with Y forms a cyclic group; and X is heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, and alkoxyalkyl. Especially preferred are such compounds where A is -H, $-NH_2$, -F, and $-CH_3$, L is -H, -F, $-OCH_3$, -Cl, and $-CH_3$, E is -H and -Cl, J is -H, halo, C1-C5 hydroxyalkyl, C1-C5 haloalkyl, C1-C5 R^8_2N-alkyl, C1-C5 alicyclic, and C1-C5 alkyl, X is $-CH_2OCH_2-$, and 2,5-furanyl, and Y is lower alkyl. Most preferred are the following such compounds and their salts, and prodrug and their salts:

1) A is $-NH_2$, L is -F, E is -H, J is -H, Y is isobutyl, and X is 2,5-furanyl;

2) A, L, and J are -H, E is -Cl, Y is isobutyl, and X is 2,5-furanyl;

3) A is $-NH_2$, L is -F, E and J are -H, Y is cyclopropylmethyl, and X is 2,5-furanyl;

4) A is $-NH_2$, L is -F, E is -H, J is ethyl, Y is isobutyl, and X is 2,5-furanyl;

5) A is $-CH_3$, L is -Cl, E and J are -H, Y is isobutyl, and X is 2,5-furanyl;

6) A is $-NH_2$, L is -F, E is -H, J is -Cl, Y is isobutyl, and X is 2,5-furanyl;

7) A is $-NH_2$, L is -F, E is -H, J is -Br, Y is isobutyl, and X is $-CH_2OCH_2$; and

8) A, L, E, and J are $-CH_3$, Y is cyclopropylmethyl, and X is 2,5-furanyl.

Also especially preferred are compounds where A is $-NH_2$, L is -F, E is -H, J is bromopropyl, bromobutyl, chlorobutyl, cyclopropyl, hydroxypropyl, or N,N-dimethylaminopropyl, and X is 2,5-furanyl. The preferred prodrug is where R^1 is pivaloyloxymethyl or its HCl salt.

In the following examples of preferred compounds, the following prodrugs are preferred:
Acyloxyalkyl esters;
Alkoxycarbonyloxyalkyl esters;
Aryl esters;
Benzyl and substituted benzyl esters;
Disulfide containing esters;
Substituted (1,3-dioxolen-2-one)methyl esters;
Substituted 3-phthalidyl esters;
Cyclic-[2'-hydroxymethyl]-1,3-propanyl diesters and hydroxy protected forms;
Lactone type esters; and all mixed esters resulted from possible combinations of above esters.
Bis-pivaloyloxymethyl esters;
Bis-isobutyryloxymethyl esters;
Cyclic-[2'-hydroxymethyl]-1,3-propanyl diester;
Cyclic-[2'-acetoxymethyl]-1,3-propanyl diester;
Cyclic-[2'-methyloxycarbonyloxymethyl]-1,3-propanyl diester;
Bis-benzoylthiomethyl esters;
Bis-benzoylthioethyl esters;
Bis-benzoyloxymethyl esters;
Bis-*p*-fluorobenzoyloxymethyl esters;
Bis-6-chloronicotinoyloxymethyl esters;
Bis-5-bromonicotinoyloxymethyl esters;
Bis-thiophenecarbonyloxymethyl esters;
Bis-2-furoyloxymethyl esters;
Bis-3-furoyloxymethyl esters;
Diphenyl esters;
Bis-(4-methoxyphenyl) esters;
Bis-(2-methoxyphenyl) esters;
Bis-(2-ethoxyphenyl) esters;
Mono-(2-ethoxyphenyl) esters;
Bis-(4-acetamidophenyl) esters;

Bis-(4-aceyloxyphenyl) esters;
Bis-(4-hydroxyphenyl) esters;
Bis-(2-acetoxyphenyl) esters;
Bis-(3-acetoxyphenyl) esters;
Bis-(4-morpholinophenyl) esters;
Bis-[4-(1-triazolophenyl) esters;
Bis-(3-*N,N*-dimethylaminophenyl) esters;
Bis-(2-tetrahydronapthyl) esters;
Bis-(3-chloro-4-methoxy)benzyl esters;
Bis-(3-bromo-4-methoxy)benzyl esters;
Bis-(3-cyano-4-methoxy)benzyl esters;
Bis-(3-chloro-4-acetoxy)benzyl esters;
Bis-(3-bromo-4-acetoxy)benzyl esters;
Bis-(3-cyano-4-acetoxy)benzyl esters;
Bis-(4-chloro)benzyl esters;
Bis-(4-acetoxy)benzyl esters;
Bis-(3,5-dimethoxy-4-acetoxy)benzyl esters;
Bis-(3-methyl-4-acetoxy)benzyl esters;
Bis-(benzyl)esters;
Bis-(3-methoxy-4-acetoxy)benzyl esters;
Bis-(3-chloro-4-acetoxy)benzyl esters;
cyclic-(2,2-dimethylpropyl)phosphonoamidate;
cyclic-(2-hydroxymethylpropyl) ester;
Bis-(6'-hydroxy-3',4'-disulfide)hexyl esters;
Bis-(6'-acetoxy-3',4'-disulfide)hexyl esters;
(3',4'-Dithia)cyclononane esters;
Bis-(5-methyl-1,3-dioxolen-2-one-4-yl)methyl esters;
Bis-(5-ethyl-1,3-dioxolen-2-one-4-yl)methyl esters;
Bis-(5-tert-butyl-1,3-dioxolen-2-one-4-yl)methyl esters;
Bis-3-(5,6,7-trimethoxy)phthalidyl esters;
Bis-(cyclohexyloxycarbonyloxymethyl) esters;
Bis-(isopropyloxycarbonyloxymethyl) esters;
Bis-(ethyloxycarbonyloxymethyl) esters;
Bis-(methyloxycarbonyloxymethyl) esters;
Bis-(isopropylthiocarbonyloxymethyl) esters;
Bis-(phenyloxycarbonyloxymethyl) esters;

Bis-(benzyloxycarbonyloxymethyl) esters;
Bis-(phenylthiocarbonyloxymethyl) esters;
Bis-(*p*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*m*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methylphenyloxycarbonyloxymethyl) esters;
Bis-(*p*-chlorophenyloxycarbonyloxymethyl) esters;
Bis-(1,4-biphenyloxycarbonyloxymethyl) esters;
Bis-[(2-phthalimidoethyl)oxycarbonyloxymethyl]esters;
Bis-(*N*-Phenyl, *N*-methylcarbamoyloxymethyl) esters;
Bis-(2-trichloroethyl) esters;
Bis-(2-bromoethyl) esters;
Bis-(2-iodoethyl) esters;
Bis-(2-azidoethyl) esters;
Bis-(2-acetoxyethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-(2-*N,N*-diaminoethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-(methoxycarbonylmethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-[*N,N*-di(2-hydroxyethyl)]amidomethylesters;
Bis-(2-aminoethyl) esters;
Bis-(2-methyl-5-thiozolomethyl) esters;
Bis-(bis-2-hydroxyethylamidomthyl) esters.

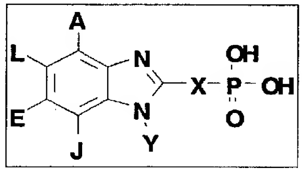
Most preferred are the following:

Bis-pivaloyloxymethyl esters;
Bis-isobutyryloxymethyl esters;
cyclic-(2-hydroxymethylpropyl) ester;
cyclic-(2-acetoxymethylpropyl) ester;
cyclic-(2-methyloxycarbonyloxymethylpropyl) ester;
cyclic-(2-cyclohexylcarbonyloxymethylpropyl)ester;
cyclic-(2-aminomethylpropyl)ester;
cyclic-(2-azidomethylpropyl)ester;
Bis-benzoylthiomethyl esters;

Bis-benzoylthioethylesters;
Bis-benzoyloxymethyl esters;
Bis-*p*-fluorobenzoyloxymethyl esters;
Bis-6-chloronicotinoyloxymethyl esters;
Bis-5-bromonicotinoyloxymethyl esters;
Bis-thiophenecarbonyloxymethyl esters;
Bis-2-furoyloxymethyl esters;
Bis-3-furoyloxymethyl esters;
Diphenyl esters;
Bis-(2-methyl)phenyl esters;
Bis-(2-methoxy)phenyl esters;
Bis-(2-ethoxy)phenyl esters;
Bis-(4-methoxy)phenyl esters;
Bis-(3-bromo-4-methoxy)benzyl esters;
Bis-(4-acetoxy)benzyl esters;
Bis-(3,5-dimethoxy-4-acetoxy)benzyl esters;
Bis-(3-methyl-4-acetoxy)benzyl esters;
Bis-(3-methoxy-4-acetoxy)benzyl esters;
Bis-(3-chloro-4-acetoxy)benzyl esters;
Bis-(cyclohexyloxycarbonyloxymethyl) esters;
Bis-(isopropyloxycarbonyloxymethyl) esters;
Bis-(ethyloxycarbonyloxymethyl) esters;
Bis-(methyloxycarbonyloxymethyl) esters;
Bis-(isopropylthiocarbonyloxymethyl) esters;
Bis-(phenyloxycarbonyloxymethyl) esters;
Bis-(benzyloxycarbonyloxymethyl) esters;
Bis-(phenylthiocarbonyloxymethyl) esters;
Bis-(*p*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*m*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methylphenyloxycarbonyloxymethyl) esters;
Bis-(*p*-chlorophenyloxycarbonyloxymethyl) esters;
Bis-(1,4-biphenyloxycarbonyloxymethyl) esters;
Bis-[(2-phthalimidoethyl)oxycarbonyloxymethyl]esters;
Bis-(6'-hydroxy-3',4'-disulfide)hexyl esters; and
(3',4'-Disulfide)cyclononane esters.

Bis-(2-bromoethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-(2-*N,N*-diaminoethyl) esters;

Examples of preferred compounds include, but are not limited to the salts and prodrugs of the compounds of Table 1.

Table Compound No.	Synthetic Example No.						
		A	L	E	J[1]	Y	X[2]
1	12.2	NH2	H	H	H	cyclohexylethyl	2,5-furanyl
2	12.3	NH2	H	H	H	H	2,5-furanyl
3	12.4	NH2	H	H	H	methyl	2,5-furanyl
4	12.5	NH2	H	H	H	4-methylbenzyl	2,5-furanyl
5	12.6	NH2	H	H	H	3-CO2Me benzyl	2,5-furanyl
6	12.1	NH2	H	H	H	Et	2,5-furanyl
7	12.8	NH2	H	H	H	Et	methoxymethyl
8	12.9	NH2	H	H	H	3-methylbenzyl	2,5-furanyl
9	12.10	NH2	H	H	H	2-(3-CO2Et-5,6,7,8-tetrahydronapthyl	2,5-furanyl
10	12.11	NH2	H	H	H	2-(3-CO2H-5,6,7,8-tetrahydronapthyl	2,5-furanyl
11	12.12	NH2	H	H	H	propyl	2,5-furanyl
12	12.13	NH2	H	H	H	norbornylmethyl	2,5-furanyl

1 In the Table for J where structures are depicted, the line on the left side is a direct attachment to the benzimidazole ring.

2 In the table for X where structures are depicted, the line on the left side is part of the benzimidazole ring, an atom or the left side is attached to the benzimidazole ring, and the line on the right side is attached directly to the P of the phosphonate.

13	12.14	NH2	H	H	H	3-CO2H benzyl	2,5-furanyl
14	12.15	NH2	H	H	H	cyclopentylmethyl	2,5-furanyl
15	12.16	NH2	H	H	H	cyclopropanemethyl	2,5-furanyl
16	12.17	NH2	H	H	H	cyclobutylmethyl	2,5-furanyl
17	12.18	NH2	H	H	H	3-methyl-6, 6-dimethyl-2-cyclohexenylmethyl	2,5-furanyl
18	12.19	NH2	H	H	H	2-methyl-2-butenyl	2,5-furanyl
19	12.20	NH2	H	H	H	1S,2S,5S-myrtanyl	2,5-furanyl
20	12.21	NH2	H	H	H	4-tBu benzyl	2,5-furanyl
21	12.22	NH2	H	H	H	cyclohexylbutyl	2,5-furanyl
22	12.23	NH2	H	H	H	cyclohexylpropyl	2,5-furanyl
23	12.24	NH2	H	H	H	3-carboxypropyl	2,5-furanyl
24	12.25	NH2	H	H	H	3-CO2Et propyl	2,5-furanyl
25	12.26	NH2	H	H	H	tBu-methylketone	2,5-furanyl
26	12.27	NH2	H	H	H	cycloheptylmethyl	2,5-furanyl
27	12.28	NH2	H	H	H	cyclohexanylmethyl	2,5-furanyl
28	12.29	NH2	H	H	H	benzyl	2,5-furanyl
29	12.30	NH2	H	H	H	3-CF3-benzyl	2,5-furanyl
30	12.31	NH2	H	H	H	3-carbamoylpropyl	2,5-furanyl
31	12.32	NH2	H	H	H	7-hydroxy-3R, 7-dimethyloctyl	2,5-furanyl
32	12.33	NH2	H	H	H	4-chlorobutyl	2,5-furanyl
33	12.34	NH2	H	H	H	4-Ph-benzyl	2,5-furanyl
34	12.35	NH2	H	H	H	3-chloropropyl	2,5-furanyl
35	12.36	NH2	H	H	H	4-hydroxybutyl	2,5-furanyl
36	12.37	NH2	H	H	H	3-furanylmethyl	2,5-furanyl
37	12.38	NH2	H	H	H	3-OH-benzyl	2,5-furanyl
38	12.39	NH2	H	H	H	2-OMe-phenethyl	2,5-furanyl
39	12.40	NH2	H	H	H	3-OMe-phenethyl	2,5-furanyl
40		Me	Cl	H	H	ethyl	2,5-furanyl
41	12.46	NH2	H	H	Br	isobutyl	2,5-furanyl
42	12.47	NH2	H	H	Br	cyclobutylmethyl	2,5-furanyl
43	12.48	NH2	Br	H	H	cyclobutylmethyl	2,5-furanyl

44	12.51	NH2	H	H	H	2-thienylethyl	2,5-furanyl
45	12.52	NH2	Et	H	H	isobutyl	2,5-furanyl
46	12.56	NH2	H	H	H	3-NH2-phenethyl	2,5-furanyl
47	12.57	NH2	H	H	H	2-Et-pentyl	methoxymethyl
48	12.59	NH2	H	H	H	H	2,5-furanyl
49	12.60	NH2	Pr	H	H	isobutyl	2,5-furanyl
50		NH2	Et	H	H	isobutyl	2,5-furanyl
51	12.62	NH2	F	H	Br	isobutyl	2,5-furanyl
52	12.53	NH2	F	H	H	isobutyl	2,5-furanyl
53	12.64	NH2	F	H	Et	isobutyl	2,5-furanyl
54	12.54	NH2	F	H	Cl	isobutyl	2,5-furanyl
55		NH2	F	H	Me	isobutyl	2,5-furanyl
56		NH2	F	H	Pr	isobutyl	2,5-furanyl
57		NH2	F	H	i-Pr	isobutyl	2,5-furanyl
58		NH2	F	H	Bu	isobutyl	2,5-furanyl
59		NH2	F	H	i-Bu	isobutyl	2,5-furanyl
60		NH2	F	H	OMe	isobutyl	2,5-furanyl
61		NH2	F	H	OEt	isobutyl	2,5-furanyl
62		NH2	F	H	SMe	isobutyl	2,5-furanyl
63		NH2	F	H	SEt	isobutyl	2,5-furanyl
64		NH2	F	H	NEt2	isobutyl	2,5-furanyl
65		NH2	F	H	NMe2	isobutyl	2,5-furanyl
66		NH2	F	H	I	isobutyl	2,5-furanyl
67		NH2	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
68		NH2	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
69		NH2	F	H	p-F Phenyl	isobutyl	2,5-furanyl
70		NH2	F	H	o-F Phenyl	isobutyl	2,5-furanyl
71		NH2	F	H	m-F Phenyl	isobutyl	2,5-furanyl
72		NH2	F	H	2-Furanyl	isobutyl	2,5-furanyl
73		NH2	F	H	2-thiophenyl	isobutyl	2,5-furanyl
74		NH2	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
75		NH2	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
76		NH2	F	H	CN	isobutyl	2,5-furanyl
77		NH2	F	H	m-Cl phenyl	isobutyl	2,5-furanyl

78		NH2	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
79		NH2	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
80		NH2	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
81		NH2	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
82		NH2	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
83		NH2	F	H	CF3	isobutyl	2,5-furanyl
84		NH2	F	H	cyclopentyl	isobutyl	2,5-furanyl
85		NH2	F	H	cyclohexyl	isobutyl	2,5-furanyl
86		NH2	F	H	cyclobutyl	isobutyl	2,5-furanyl
87		NH2	F	H	cyclopropyl	isobutyl	2,5-furanyl
88		NH2	F	H	Phenyl	isobutyl	2,5-furanyl
89		NH2	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
90		NH2	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
91		NH2	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
92		NH2	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
93		NH2	F	Cl	F	isobutyl	2,5-furanyl
94		NH2	F	Cl	Me	isobutyl	2,5-furanyl
95		NH2	F	Cl	Pr	isobutyl	2,5-furanyl
96		NH2	F	Cl	i-Pr	isobutyl	2,5-furanyl
97		NH2	F	Cl	Bu	isobutyl	2,5-furanyl
98		NH2	F	Cl	i-Bu	isobutyl	2,5-furanyl
99		NH2	F	Cl	OMe	isobutyl	2,5-furanyl
100		NH2	F	Cl	OEt	isobutyl	2,5-furanyl
101		NH2	F	Cl	SMe	isobutyl	2,5-furanyl
102		NH2	F	Cl	SEt	isobutyl	2,5-furanyl
103		NH2	F	Cl	NEt2	isobutyl	2,5-furanyl
104		NH2	F	Cl	NMe2	isobutyl	2,5-furanyl
105		NH2	F	Cl	I	isobutyl	2,5-furanyl
106		NH2	F	Cl	m-OMePhenyl	isobutyl	2,5-furanyl
107		NH2	F	Cl	o-OMePhenyl	isobutyl	2,5-furanyl
108		NH2	F	Cl	p-F Phenyl	isobutyl	2,5-furanyl
109		NH2	F	Cl	o-F Phenyl	isobutyl	2,5-furanyl
110		NH2	F	Cl	m-F Phenyl	isobutyl	2,5-furanyl
111		NH2	F	Cl	2-Furanyl	isobutyl	2,5-furanyl

112		NH2	F	Cl	2-thiophenyl	isobutyl	2,5-furanyl
113		NH2	F	Cl	2-Furanylmethyl	isobutyl	2,5-furanyl
114		NH2	F	Cl	2-Thiophenylmethyl	isobutyl	2,5-furanyl
115		NH2	F	Cl	CN	isobutyl	2,5-furanyl
116		NH2	F	Cl	m-Cl phenyl	isobutyl	2,5-furanyl
117		NH2	F	Cl	p-Cl phenyl	isobutyl	2,5-furanyl
118		NH2	F	Cl	o-Cl phenyl	isobutyl	2,5-furanyl
119		NH2	F	Cl	m-Br Phenyl	isobutyl	2,5-furanyl
120		NH2	F	Cl	p-Br Phenyl	isobutyl	2,5-furanyl
121		NH2	F	Cl	o-Br Phenyl	isobutyl	2,5-furanyl
122		NH2	F	Cl	CF3	isobutyl	2,5-furanyl
123		NH2	F	Cl	cyclopentyl	isobutyl	2,5-furanyl
124		NH2	F	Cl	cyclohexyl	isobutyl	2,5-furanyl
125		NH2	F	Cl	cyclobutyl	isobutyl	2,5-furanyl
126		NH2	F	Cl	cyclopropyl	isobutyl	2,5-furanyl
127		NH2	F	Cl	Phenyl	isobutyl	2,5-furanyl
128		NH2	F	SMe	Et	isobutyl	2,5-furanyl
129		NH2	F	SMe	Cl	isobutyl	2,5-furanyl
130		NH2	F	SMe	Br	isobutyl	2,5-furanyl
131		NH2	F	SMe	Me	isobutyl	2,5-furanyl
132		NH2	F	SMe	Pr	isobutyl	2,5-furanyl
133		NH2	F	SMe	i-Pr	isobutyl	2,5-furanyl
134		NH2	F	SMe	Bu	isobutyl	2,5-furanyl
135		NH2	F	SMe	i-Bu	isobutyl	2,5-furanyl
136		NH2	F	SMe	OMe	isobutyl	2,5-furanyl
137		NH2	F	SMe	OEt	isobutyl	2,5-furanyl
138		NH2	F	SMe	SMe	isobutyl	2,5-furanyl
139		NH2	F	SMe	SEt	isobutyl	2,5-furanyl
140		NH2	F	SMe	NEt2	isobutyl	2,5-furanyl
141		NH2	F	SMe	NMe2	isobutyl	2,5-furanyl
142		NH2	F	SMe	I	isobutyl	2,5-furanyl
143		NH2	F	SMe	m-OMePhenyl	isobutyl	2,5-furanyl
144		NH2	F	SMe	o-OMePhenyl	isobutyl	2,5-furanyl
145		NH2	F	SMe	p-F Phenyl	isobutyl	2,5-furanyl

146		NH2	F	SMe	o-F Phenyl	isobutyl	2,5-furanyl
147		NH2	F	SMe	m-F Phenyl	isobutyl	2,5-furanyl
148		NH2	F	SMe	2-Furanyl	isobutyl	2,5-furanyl
149		NH2	F	SMe	2-thiophenyl	isobutyl	2,5-furanyl
150		NH2	F	SMe	2-Furanylmethyl	isobutyl	2,5-furanyl
151		NH2	F	SMe	2-Thiophenylmethyl	isobutyl	2,5-furanyl
152		NH2	F	SMe	CN	isobutyl	2,5-furanyl
153		NH2	F	SMe	m-Cl phenyl	isobutyl	2,5-furanyl
154		NH2	F	SMe	p-Cl phenyl	isobutyl	2,5-furanyl
155		NH2	F	SMe	o-Cl phenyl	isobutyl	2,5-furanyl
156		NH2	F	SMe	m-Br Phenyl	isobutyl	2,5-furanyl
157		NH2	F	SMe	p-Br Phenyl	isobutyl	2,5-furanyl
158		NH2	F	SMe	o-Br Phenyl	isobutyl	2,5-furanyl
159		NH2	F	SMe	CF3	isobutyl	2,5-furanyl
160		NH2	F	SMe	cyclopentyl	isobutyl	2,5-furanyl
161		NH2	F	SMe	cyclohexyl	isobutyl	2,5-furanyl
162		NH2	F	SMe	cyclobutyl	isobutyl	2,5-furanyl
163		NH2	F	SMe	Phenyl	isobutyl	2,5-furanyl
164		NH2	F	H	F	neopentyl	2,5-furanyl
165		NH2	F	H	Me	neopentyl	2,5-furanyl
166		NH2	F	H	Pr	neopentyl	2,5-furanyl
167		NH2	F	H	i-Pr	neopentyl	2,5-furanyl
168		NH2	F	H	Bu	neopentyl	2,5-furanyl
169		NH2	F	H	i-Bu	neopentyl	2,5-furanyl
170		NH2	F	H	OMe	neopentyl	2,5-furanyl
171		NH2	F	H	OEt	neopentyl	2,5-furanyl
172		NH2	F	H	SMe	neopentyl	2,5-furanyl
173		NH2	F	H	SEt	neopentyl	2,5-furanyl
174		NH2	F	H	NEt2	neopentyl	2,5-furanyl
175		NH2	F	H	NMe2	neopentyl	2,5-furanyl
176		NH2	F	H	I	neopentyl	2,5-furanyl
177		NH2	F	H	m-OMePhenyl	neopentyl	2,5-furanyl
178		NH2	F	H	o-OMePhenyl	neopentyl	2,5-furanyl
179		NH2	F	H	p-F Phenyl	neopentyl	2,5-furanyl

180		NH2	F	H	o-F Phenyl	neopentyl	2,5-furanyl
181		NH2	F	H	m-F Phenyl	neopentyl	2,5-furanyl
182		NH2	F	H	2-Furanyl	neopentyl	2,5-furanyl
183		NH2	F	H	2-thiophenyl	neopentyl	2,5-furanyl
184		NH2	F	H	2-Furanylmethyl	neopentyl	2,5-furanyl
185		NH2	F	H	2-Thiophenylmethyl	neopentyl	2,5-furanyl
186		NH2	F	H	CN	neopentyl	2,5-furanyl
187		NH2	F	H	m-Cl phenyl	neopentyl	2,5-furanyl
188		NH2	F	H	p-Cl phenyl	neopentyl	2,5-furanyl
189		NH2	F	H	o-Cl phenyl	neopentyl	2,5-furanyl
190		NH2	F	H	m-Br Phenyl	neopentyl	2,5-furanyl
191		NH2	F	H	p-Br Phenyl	neopentyl	2,5-furanyl
192		NH2	F	H	o-Br Phenyl	neopentyl	2,5-furanyl
193		NH2	F	H	CF3	neopentyl	2,5-furanyl
194		NH2	F	H	Phenyl	neopentyl	2,5-furanyl
195		NH2	F	H	cyclopentyl	neopentyl	2,5-furanyl
196		NH2	F	H	cyclohexyl	neopentyl	2,5-furanyl
197		NH2	F	H	cyclobutyl	neopentyl	2,5-furanyl
198		NH2	F	H	cyclopropyl	neopentyl	2,5-furanyl
199	12.61	NH2	F	H	H	cyclopropylmethyl	2,5-furanyl
200		NH2	F	H	F	cyclopropylmethyl	2,5-furanyl
201		NH2	F	H	Me	cyclopropylmethyl	2,5-furanyl
202		NH2	F	H	Pr	cyclopropylmethyl	2,5-furanyl
203		NH2	F	H	i-Pr	cyclopropylmethyl	2,5-furanyl
204		NH2	F	H	Bu	cyclopropylmethyl	2,5-furanyl
205		NH2	F	H	i-Bu	cyclopropylmethyl	2,5-furanyl
206		NH2	F	H	OMe	cyclopropylmethyl	2,5-furanyl
207		NH2	F	H	OEt	cyclopropylmethyl	2,5-furanyl
208		NH2	F	H	SMe	cyclopropylmethyl	2,5-furanyl
209		NH2	F	H	SEt	cyclopropylmethyl	2,5-furanyl
210		NH2	F	H	NEt2	cyclopropylmethyl	2,5-furanyl
211		NH2	F	H	NMe2	cyclopropylmethyl	2,5-furanyl
212		NH2	F	H	I	cyclopropylmethyl	2,5-furanyl
213		NH2	F	H	m-OMePhenyl	cyclopropylmethyl	2,5-furanyl

214		NH2	F	H	o-OMePhenyl	cyclopropylmethyl	2,5-furanyl
215		NH2	F	H	p-F Phenyl	cyclopropylmethyl	2,5-furanyl
216		NH2	F	H	o-F Phenyl	cyclopropylmethyl	2,5-furanyl
217		NH2	F	H	m-F Phenyl	cyclopropylmethyl	2,5-furanyl
218		NH2	F	H	2-Furanyl	cyclopropylmethyl	2,5-furanyl
219		NH2	F	H	2-thiophenyl	cyclopropylmethyl	2,5-furanyl
220		NH2	F	H	2-Furanylmethyl	cyclopropylmethyl	2,5-furanyl
221		NH2	F	H	2-Thiophenylmethyl	cyclopropylmethyl	2,5-furanyl
222		NH2	F	H	CN	cyclopropylmethyl	2,5-furanyl
223		NH2	F	H	m-Cl phenyl	cyclopropylmethyl	2,5-furanyl
224		NH2	F	H	p-Cl phenyl	cyclopropylmethyl	2,5-furanyl
225		NH2	F	H	o-Cl phenyl	cyclopropylmethyl	2,5-furanyl
226		NH2	F	H	m-Br Phenyl	cyclopropylmethyl	2,5-furanyl
227		NH2	F	H	p-Br Phenyl	cyclopropylmethyl	2,5-furanyl
228		NH2	F	H	o-Br Phenyl	cyclopropylmethyl	2,5-furanyl
229		NH2	F	H	CF3	cyclopropylmethyl	2,5-furanyl
230		NH2	F	H	Phenyl	cyclopropylmethyl	2,5-furanyl
231		NH2	F	H	cyclopentyl	neopentyl	2,5-furanyl
232		NH2	F	H	cyclohexyl	neopentyl	2,5-furanyl
233		NH2	F	H	cyclobutyl	neopentyl	2,5-furanyl
234		NH2	F	H	cyclopropyl	neopentyl	2,5-furanyl
235		NH2	F	H	cyclopentylmethyl	neopentyl	2,5-furanyl
236		NH2	F	H	cyclohexylmethyl	neopentyl	2,5-furanyl
237		NH2	F	H	cyclobutylmethyl	neopentyl	2,5-furanyl
238		NH2	F	H	cyclopropylmethyl	neopentyl	2,5-furanyl
239		NH2	F	H	F	cyclobutylmethyl	2,5-furanyl
240		NH2	F	H	Me	cyclobutylmethyl	2,5-furanyl
241		NH2	F	H	Pr	cyclobutylmethyl	2,5-furanyl
242		NH2	F	H	i-Pr	cyclobutylmethyl	2,5-furanyl
243		NH2	F	H	Bu	cyclobutylmethyl	2,5-furanyl
244		NH2	F	H	i-Bu	cyclobutylmethyl	2,5-furanyl
245		NH2	F	H	OMe	cyclobutylmethyl	2,5-furanyl
246		NH2	F	H	OEt	cyclobutylmethyl	2,5-furanyl
247		NH2	F	H	SMe	cyclobutylmethyl	2,5-furanyl

248		NH2	F	H	SEt	cyclobutylmethyl	2,5-furanyl
249		NH2	F	H	NEt2	cyclobutylmethyl	2,5-furanyl
250		NH2	F	H	NMe2	cyclobutylmethyl	2,5-furanyl
251		NH2	F	H	I	cyclobutylmethyl	2,5-furanyl
252		NH2	F	H	m-OMePhenyl	cyclobutylmethyl	2,5-furanyl
253		NH2	F	H	o-OMePhenyl	cyclobutylmethyl	2,5-furanyl
254		NH2	F	H	p-F Phenyl	cyclobutylmethyl	2,5-furanyl
255		NH2	F	H	o-F Phenyl	cyclobutylmethyl	2,5-furanyl
256		NH2	F	H	m-F Phenyl	cyclobutylmethyl	2,5-furanyl
257		NH2	F	H	2-Furanyl	cyclobutylmethyl	2,5-furanyl
258		NH2	F	H	2-thiophenyl	cyclobutylmethyl	2,5-furanyl
259		NH2	F	H	2-Furanylmethyl	cyclobutylmethyl	2,5-furanyl
260		NH2	F	H	2-Thiophenylmethyl	cyclobutylmethyl	2,5-furanyl
261		NH2	F	H	CN	cyclobutylmethyl	2,5-furanyl
262		NH2	F	H	m-Cl phenyl	cyclobutylmethyl	2,5-furanyl
263		NH2	F	H	p-Cl phenyl	cyclobutylmethyl	2,5-furanyl
264		NH2	F	H	o-Cl phenyl	cyclobutylmethyl	2,5-furanyl
265		NH2	F	H	m-Br Phenyl	cyclobutylmethyl	2,5-furanyl
266		NH2	F	H	p-Br Phenyl	cyclobutylmethyl	2,5-furanyl
267		NH2	F	H	o-Br Phenyl	cyclobutylmethyl	2,5-furanyl
268		NH2	F	H	CF3	cyclobutylmethyl	2,5-furanyl
269		NH2	F	H	Phenyl	cyclobutylmethyl	2,5-furanyl
270		NH2	F	F	F	isobutyl	2,5-furanyl
271	12.63	NH2	F	Cl	H	isobutyl	2,5-furanyl
272		NH2	F	F	Et	isobutyl	2,5-furanyl
273		NH2	F	Cl	Et	isobutyl	2,5-furanyl
274		NH2	F	H	Et	cyclopropylmethyl	2,5-furanyl
275		NH2	F	H	Et	cyclobutylmethyl	2,5-furanyl
276		NH2	F	Me	H	isobutyl	2,5-furanyl
277		NH2	F	Me	Me	Isobutyl	2,5-furanyl
278		NH2	F	Me	Et	Isobutyl	2,5-furanyl
279		NH2	F	F	Pr	isobutyl	2,5-furanyl
280		NH2	F	Me	Pr	isobutyl	2,5-furanyl
281		NH2	F	Cl	Pr	isobutyl	2,5-furanyl

282		NH2	F	H	H	isobutyl	methoxymethyl
283		NH2	F	H	H	cyclopropylmethyl	methoxymethyl
284		NH2	F	H	Et	isobutyl	methoxymethyl
285		NH2	F	H	Et	cyclopropylmethyl	methoxymethyl
286		OH	F	H	F	isobutyl	2,5-furanyl
287		OH	F	H	Me	isobutyl	2,5-furanyl
288		OH	F	H	Pr	isobutyl	2,5-furanyl
289		OH	F	H	i-Pr	isobutyl	2,5-furanyl
290		OH	F	H	Bu	isobutyl	2,5-furanyl
291		OH	F	H	i-Bu	isobutyl	2,5-furanyl
292		OH	F	H	OMe	isobutyl	2,5-furanyl
293		OH	F	H	OEt	isobutyl	2,5-furanyl
294		OH	F	H	SMe	isobutyl	2,5-furanyl
295		OH	F	H	SEt	isobutyl	2,5-furanyl
296		OH	F	H	NEt2	isobutyl	2,5-furanyl
297		OH	F	H	NMe2	isobutyl	2,5-furanyl
298		OH	F	H	I	isobutyl	2,5-furanyl
299		OH	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
300		OH	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
301		OH	F	H	p-F Phenyl	isobutyl	2,5-furanyl
302		OH	F	H	o-F Phenyl	isobutyl	2,5-furanyl
303		OH	F	H	m-F Phenyl	isobutyl	2,5-furanyl
304		OH	F	H	2-Furanyl	isobutyl	2,5-furanyl
305		OH	F	H	2-thiophenyl	isobutyl	2,5-furanyl
306		OH	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
307		OH	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
308		OH	F	H	CN	isobutyl	2,5-furanyl
309		OH	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
310		OH	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
311		OH	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
312		OH	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
313		OH	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
314		OH	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
315		OH	F	H	CF3	isobutyl	2,5-furanyl

316		OH	F	H	Phenyl	isobutyl	2,5-furanyl
317		OH	F	H	Cl	isobutyl	2,5-furanyl
318		OH	F	H	Br	isobutyl	2,5-furanyl
319		OH	F	H	Et	isobutyl	2,5-furanyl
320		NH2	F	F	Cl	isobutyl	2,5-furanyl
321		NH2	F	F	Br	isobutyl	2,5-furanyl
322	13.51	NH2	OH	H	H	isobutyl	2,5-furanyl
323		NH2	OH	H	F	isobutyl	2,5-furanyl
324		NH2	OH	H	Me	isobutyl	2,5-furanyl
325		NH2	OH	H	Pr	isobutyl	2,5-furanyl
326		NH2	OH	H	i-Pr	isobutyl	2,5-furanyl
327		NH2	OH	H	Bu	isobutyl	2,5-furanyl
328		NH2	OH	H	i-Bu	isobutyl	2,5-furanyl
329		NH2	OH	H	OMe	isobutyl	2,5-furanyl
330		NH2	OH	H	OEt	isobutyl	2,5-furanyl
331		NH2	OH	H	SMe	isobutyl	2,5-furanyl
332		NH2	OH	H	SEt	isobutyl	2,5-furanyl
333		NH2	OH	H	NEt2	isobutyl	2,5-furanyl
334		NH2	OH	H	NMe2	isobutyl	2,5-furanyl
335		NH2	OH	H	I	isobutyl	2,5-furanyl
336		NH2	OH	H	m-OMePhenyl	isobutyl	2,5-furanyl
337		NH2	OH	H	o-OMePhenyl	isobutyl	2,5-furanyl
338		NH2	OH	H	p-F Phenyl	isobutyl	2,5-furanyl
339		NH2	OH	H	o-F Phenyl	isobutyl	2,5-furanyl
340		NH2	OH	H	m-F Phenyl	isobutyl	2,5-furanyl
341		NH2	OH	H	2-Furanyl	isobutyl	2,5-furanyl
342		NH2	OH	H	2-thiophenyl	isobutyl	2,5-furanyl
343		NH2	OH	H	2-Furanylmethyl	isobutyl	2,5-furanyl
344		NH2	OH	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
345		NH2	OH	H	CN	isobutyl	2,5-furanyl
346		NH2	OH	H	m-Cl phenyl	isobutyl	2,5-furanyl
347		NH2	OH	H	p-Cl phenyl	isobutyl	2,5-furanyl
348		NH2	OH	H	o-Cl phenyl	isobutyl	2,5-furanyl
349		NH2	OH	H	m-Br Phenyl	isobutyl	2,5-furanyl

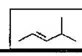
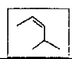
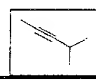
350		NH2	OH	H	p-Br Phenyl	isobutyl	2,5-furanyl
351		NH2	OH	H	o-Br Phenyl	isobutyl	2,5-furanyl
352		NH2	OH	H	CF3	isobutyl	2,5-furanyl
353		NH2	OH	H	Phenyl	isobutyl	2,5-furanyl
354	12.55	NH2	OMe	H	H	isobutyl	2,5-furanyl
355		NH2	OMe	H	F	isobutyl	2,5-furanyl
356		NH2	OMe	H	Me	isobutyl	2,5-furanyl
357		NH2	OMe	H	Pr	isobutyl	2,5-furanyl
358		NH2	OMe	H	i-Pr	isobutyl	2,5-furanyl
359		NH2	OMe	H	Bu	isobutyl	2,5-furanyl
360		NH2	OMe	H	i-Bu	isobutyl	2,5-furanyl
361		NH2	OMe	H	OMe	isobutyl	2,5-furanyl
362		NH2	OMe	H	OEt	isobutyl	2,5-furanyl
363		NH2	OMe	H	SMe	isobutyl	2,5-furanyl
364		NH2	OMe	H	SEt	isobutyl	2,5-furanyl
365		NH2	OMe	H	NEt2	isobutyl	2,5-furanyl
366		NH2	OMe	H	NMe2	isobutyl	2,5-furanyl
367		NH2	OMe	H	I	isobutyl	2,5-furanyl
368		NH2	OMe	H	m-OMePhenyl	isobutyl	2,5-furanyl
369		NH2	OMe	H	o-OMePhenyl	isobutyl	2,5-furanyl
370		NH2	OMe	H	p-F Phenyl	isobutyl	2,5-furanyl
371		NH2	OMe	H	o-F Phenyl	isobutyl	2,5-furanyl
372		NH2	OMe	H	m-F Phenyl	isobutyl	2,5-furanyl
373		NH2	OMe	H	2-Furanyl	isobutyl	2,5-furanyl
374		NH2	OMe	H	2-thiophenyl	isobutyl	2,5-furanyl
375		NH2	OMe	H	2-Furanylmethyl	isobutyl	2,5-furanyl
376		NH2	OMe	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
377		NH2	OMe	H	CN	isobutyl	2,5-furanyl
378		NH2	OMe	H	m-Cl phenyl	isobutyl	2,5-furanyl
379		NH2	OMe	H	p-Cl phenyl	isobutyl	2,5-furanyl
380		NH2	OMe	H	o-Cl phenyl	isobutyl	2,5-furanyl
381		NH2	OMe	H	m-Br Phenyl	isobutyl	2,5-furanyl
382		NH2	OMe	H	p-Br Phenyl	isobutyl	2,5-furanyl
383		NH2	OMe	H	o-Br Phenyl	isobutyl	2,5-furanyl

384		NH2	OMe	H	CF3	isobutyl	2,5-furanyl
385		NH2	OMe	H	Phenyl	isobutyl	2,5-furanyl
386		NH2	Cl	H	F	isobutyl	2,5-furanyl
387		NH2	Cl	H	Me	isobutyl	2,5-furanyl
388		NH2	Cl	H	Pr	isobutyl	2,5-furanyl
389		NH2	Cl	H	i-Pr	isobutyl	2,5-furanyl
390		NH2	Cl	H	Bu	isobutyl	2,5-furanyl
391		NH2	Cl	H	i-Bu	isobutyl	2,5-furanyl
392		NH2	Cl	H	OMe	isobutyl	2,5-furanyl
393		NH2	Cl	H	OEt	isobutyl	2,5-furanyl
394		NH2	Cl	H	SMe	isobutyl	2,5-furanyl
395		NH2	Cl	H	SEt	isobutyl	2,5-furanyl
396		NH2	Cl	H	NEt2	isobutyl	2,5-furanyl
397		NH2	Cl	H	NMe2	isobutyl	2,5-furanyl
398		NH2	Cl	H	I	isobutyl	2,5-furanyl
399		NH2	Cl	H	m-OMePhenyl	isobutyl	2,5-furanyl
400		NH2	Cl	H	o-OMePhenyl	isobutyl	2,5-furanyl
401		NH2	Cl	H	p-F Phenyl	isobutyl	2,5-furanyl
402		NH2	Cl	H	o-F Phenyl	isobutyl	2,5-furanyl
403		NH2	Cl	H	m-F Phenyl	isobutyl	2,5-furanyl
404		NH2	Cl	H	2-Furanyl	isobutyl	2,5-furanyl
405		NH2	Cl	H	2-thiophenyl	isobutyl	2,5-furanyl
406		NH2	Cl	H	2-Furanylmethyl	isobutyl	2,5-furanyl
407		NH2	Cl	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
408		NH2	Cl	H	CN	isobutyl	2,5-furanyl
409		NH2	Cl	H	m-Cl phenyl	isobutyl	2,5-furanyl
410		NH2	Cl	H	p-Cl phenyl	isobutyl	2,5-furanyl
411		NH2	Cl	H	o-Cl phenyl	isobutyl	2,5-furanyl
412		NH2	Cl	H	m-Br Phenyl	isobutyl	2,5-furanyl
413		NH2	Cl	H	p-Br Phenyl	isobutyl	2,5-furanyl
414		NH2	Cl	H	o-Br Phenyl	isobutyl	2,5-furanyl
415		NH2	Cl	H	CF3	isobutyl	2,5-furanyl
416		NH2	Cl	H	Phenyl	isobutyl	2,5-furanyl
417		NH2	Cl	H	Et	isobutyl	2,5-furanyl

418		NH2	Cl	H	Br	isobutyl	2,5-furanyl
419	12.50	NH2	Cl	H	Cl	isobutyl	2,5-furanyl
420	12.49	NH2	Cl	H	H	isobutyl	2,5-furanyl
421	12.58	NH2	Br	Cl	Cl	isobutyl	2,5-furanyl
422		NH2	Br	H	Cl	isobutyl	2,5-furanyl
423	12.44	NH2	Br	H	H	isobutyl	2,5-furanyl
424	12.42	NH2	Br	H	Br	isobutyl	2,5-furanyl
425		NH2	Br	H	F	isobutyl	2,5-furanyl
426		NH2	Br	H	Me	isobutyl	2,5-furanyl
427		NH2	Br	H	Pr	isobutyl	2,5-furanyl
428		NH2	Br	H	i-Pr	isobutyl	2,5-furanyl
429		NH2	Br	H	Bu	isobutyl	2,5-furanyl
430		NH2	Br	H	i-Bu	isobutyl	2,5-furanyl
431		NH2	Br	H	OMe	isobutyl	2,5-furanyl
432		NH2	Br	H	OEt	isobutyl	2,5-furanyl
433		NH2	Br	H	SMe	isobutyl	2,5-furanyl
434		NH2	Br	H	SEt	isobutyl	2,5-furanyl
435		NH2	Br	H	NEt2	isobutyl	2,5-furanyl
436		NH2	Br	H	NMe2	isobutyl	2,5-furanyl
437		NH2	Br	H	I	isobutyl	2,5-furanyl
438		NH2	Br	H	m-OMePhenyl	isobutyl	2,5-furanyl
439		NH2	Br	H	o-OMePhenyl	isobutyl	2,5-furanyl
440		NH2	Br	H	p-F Phenyl	isobutyl	2,5-furanyl
441		NH2	Br	H	o-F Phenyl	isobutyl	2,5-furanyl
442		NH2	Br	H	m-F Phenyl	isobutyl	2,5-furanyl
443		NH2	Br	H	2-Furanyl	isobutyl	2,5-furanyl
444		NH2	Br	H	2-thiophenyl	isobutyl	2,5-furanyl
445		NH2	Br	H	2-Furanylmethyl	isobutyl	2,5-furanyl
446		NH2	Br	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
447		NH2	Br	H	CN	isobutyl	2,5-furanyl
448		NH2	Br	H	m-Cl phenyl	isobutyl	2,5-furanyl
449		NH2	Br	H	p-Cl phenyl	isobutyl	2,5-furanyl
450		NH2	Br	H	o-Cl phenyl	isobutyl	2,5-furanyl
451		NH2	Br	H	m-Br Phenyl	isobutyl	2,5-furanyl

452		NH2	Br	H	p-Br Phenyl	isobutyl	2,5-furanyl
453		NH2	Br	H	o-Br Phenyl	isobutyl	2,5-furanyl
454		NH2	Br	H	CF3	isobutyl	2,5-furanyl
455		NH2	Br	H	Phenyl	isobutyl	2,5-furanyl
456		NH2	Br	H	Cl	isobutyl	2,5-furanyl
457		NH2	Br	H	Et	isobutyl	2,5-furanyl
458		NH2	Br	Cl	Cl	isobutyl	2,5-furanyl
459		NH2	Br	Cl	F	isobutyl	2,5-furanyl
460		NH2	Br	F	Cl	isobutyl	2,5-furanyl
461	12.65	Et	H	F	NH2	isobutyl	2,5-furanyl
462	13.1	H	H	H	H	H	2,5-furanyl
463	13.2	H	H	H	H	isobutyl	2,5-furanyl
464	13.6	H	CF3	H	H	H	2,5-furanyl
465	13.7	H	F	H	H	H	2,5-furanyl
466	13.8	H	Cl	Cl	H	H	2,5-furanyl
467	13.9	H	Cl	H	H	H	2,5-furanyl
468	13.10	H	Me	H	H	H	2,5-furanyl
469	13.11	H	t-Bu	H	H	H	2,5-furanyl
470	13.12	H	H	H	H	Ph	2,5-furanyl
471	13.13	H	H	H	H	2-CO2H-Phenyl	2,5-furanyl
472	13.14	H	NO2	H	H	H	2,5-furanyl
473	13.15	Me	Me	H	H	H	2,5-furanyl
474	13.16	H	Cl	H	H	isobutyl	2,5-furanyl
475	13.17	H	H	Cl	H	isobutyl	2,5-furanyl
476	13.18	H	C6H5CO	H	H	H	2,5-furanyl
477	13.19	amidino-methyl	H	H	H	2-ethylpentyl	2,5-furanyl
478	13.20	iso-butyloxy	H	H	H	isobutyl	2,5-furanyl
479	13.21	OH	H	H	H	isobutyl	2,5-furanyl
480	13.22	H	F	F	H	H	2,5-furanyl
481	13.23	H	CO2Me	H	H	H	2,5-furanyl
482	13.24	H	Me	Me	H	H	2,5-furanyl
483	13.25	F	H	H	H	neopentyl	2,5-furanyl

484	13.27	H	H	F	H	isobutyl	2,5-furanyl
485	13.28	H	F	H	H	isobutyl	2,5-furanyl
486		pyridyl	H	H	H	H	2,5-furanyl
487	13.32	Me	H	H	H	H	2,5-furanyl
488	13.33	H	Cl	H	H	isopropyl	2,5-furanyl
489	13.35	H	Br	H	H	H	2,5-furanyl
490	13.36	H	Br	H	H	isobutyl	2,5-furanyl
491	13.37	H	H	Br	H	isobutyl	2,5-furanyl
492	13.38	Cl	H	Cl	H	H	2,5-furanyl
493	13.39	Cl	H	Cl	H	isobutyl	2,5-furanyl
494		H	H	H	H	Ph	2,5-furanyl
495	13.40	H	Cl	H	H	Ph	2,5-furanyl
496	13.41	H	H	Cl	H	Ph	2,5-furanyl
497	13.42	Br	H	Br	H	H	2,5-furanyl
498	13.43	Br	H	Br	H	isobutyl	2,5-furanyl
499	13.44	H	Cl	Cl	H	isobutyl	2,5-furanyl
500	13.45	H	Cl	Cl	H	cyclopropylmethyl	2,5-furanyl
501	13.46	H	Cl	F	H	H	2,5-furanyl
502	13.47	Ph	H	CF3	H	H	2,5-furanyl
503	13.48	Br	H	CF3	H	H	2,5-furanyl
504	13.49	H	Cl	F	H	cyclopropylmethyl	2,5-furanyl
505	13.50	H	Cl	F	H	isobutyl	2,5-furanyl
506	13.53	Me	Me	Br	H	isobutyl	2,5-furanyl
507	13.54	Me	H	H	H	isobutyl	2,5-furanyl
508		Me	H	H	H	neopentyl	2,5-furanyl
509		H	H	Cl	Br	isobutyl	2,5-furanyl
510		H	H	Cl	Br	isobutyl	2,5-furanyl
511		H	H	Cl	OH	isobutyl	2,5-furanyl
512		H	H	Cl	OMe	isobutyl	2,5-furanyl
513		H	H	Cl	CN	isobutyl	2,5-furanyl
514		H	H	Cl	CO2H	isobutyl	2,5-furanyl
515		H	H	Cl	CO2Me	isobutyl	2,5-furanyl
516		H	H	Cl	CONH2	isobutyl	2,5-furanyl
517		H	H	Cl	NHCONH2	isobutyl	2,5-furanyl

518		H	H	Cl	Me	isobutyl	2,5-furanyl
519		H	H	Cl	Et	isobutyl	2,5-furanyl
520		H	H	Cl	n-Pr	isobutyl	2,5-furanyl
521		H	H	Cl	i-Pr	isobutyl	2,5-furanyl
522		H	H	Cl	n-Bu	isobutyl	2,5-furanyl
523		H	H	Cl	i-butyl	isobutyl	2,5-furanyl
524		H	H	Cl	n-pentyl	isobutyl	2,5-furanyl
525		H	H	Cl	i-pentyl	isobutyl	2,5-furanyl
526		H	H	Cl	neo pentyl	isobutyl	2,5-furanyl
527		H	H	Cl	2-chloroethyl	isobutyl	2,5-furanyl
528		H	H	Cl	2-bromoethyl	isobutyl	2,5-furanyl
529		H	H	Cl	2-hydroxyethyl	isobutyl	2,5-furanyl
530		H	H	Cl	2-carboxyethyl	isobutyl	2,5-furanyl
531		H	H	Cl	2-carboxyamidoethyl	isobutyl	2,5-furanyl
532		H	H	Cl	3-carboxypropyl	isobutyl	2,5-furanyl
533		H	H	Cl	3-carboxyamidopropyl	isobutyl	2,5-furanyl
534		H	H	Cl		isobutyl	2,5-furanyl
535		H	H	Cl		isobutyl	2,5-furanyl
536		H	H	Cl		isobutyl	2,5-furanyl
537		H	H	Cl	Cyclopentyl	isobutyl	2,5-furanyl
538		H	H	Cl	Cyclopentylmethyl	isobutyl	2,5-furanyl
539		H	H	Cl	Cyclopentylethyl	isobutyl	2,5-furanyl
540		H	H	Cl	Phenyl	isobutyl	2,5-furanyl
541		H	H	Cl	benzyl	isobutyl	2,5-furanyl
542		H	H	Cl	phenethyl	isobutyl	2,5-furanyl
543		H	H	Cl	m-chlorophenyl	isobutyl	2,5-furanyl
544		H	H	Cl	p-chlorophenyl	isobutyl	2,5-furanyl
545		H	H	Cl	m-bromophenyl	isobutyl	2,5-furanyl

546		H	H	Cl	p-bromophenyl	isobutyl	2,5-furanyl
547		H	H	Cl	m-hydroxyphenyl	isobutyl	2,5-furanyl
548		H	H	Cl	p-hydroxyphenyl	isobutyl	2,5-furanyl
549		H	H	Cl	m-carboxyphenyl	isobutyl	2,5-furanyl
550		H	H	Cl	p-carboxyphenyl	isobutyl	2,5-furanyl
551		H	H	Cl	m-carboxyamidophenyl	isobutyl	2,5-furanyl
552		H	H	Cl	p-carboxyamidophenyl	isobutyl	2,5-furanyl
553		H	H	Cl	N-pyrrolidinyl	isobutyl	2,5-furanyl
554		H	H	Cl	N-thiomorpholinyl	isobutyl	2,5-furanyl
555		H	H	Cl	N-imidazolyl	isobutyl	2,5-furanyl
556		H	H	Cl	N-piperdinylmethyl	isobutyl	2,5-furanyl
557		H	H	Cl	N-piperazinylmethyl	isobutyl	2,5-furanyl
558		H	H	Cl	N-morpholinylmethyl	isobutyl	2,5-furanyl
559		H	H	Cl	N-pyrrolidinemythyl	isobutyl	2,5-furanyl
560		H	H	Cl	N-piperdinylethyl	isobutyl	2,5-furanyl
561		H	H	Cl	N-piperazinylethyl	isobutyl	2,5-furanyl
562		H	H	Cl	N-morpholinylethyl	isobutyl	2,5-furanyl
563		H	H	Cl	4-imdazolylethyl	isobutyl	2,5-furanyl
564		H	H	Cl	4-oxazolylethyl	isobutyl	2,5-furanyl
565		H	H	Cl	4-thiazolylethyl	isobutyl	2,5-furanyl
566		H	H	Cl	4-pyrimidylethyl	isobutyl	2,5-furanyl
567		H	H	Cl	5-pyrimidylethyl	isobutyl	2,5-furanyl
568		F	H	Cl	H	isobutyl	2,5-furanyl
569		Me	H	Cl	H	isobutyl	2,5-furanyl
570		Et	H	Cl	H	isobutyl	2,5-furanyl
571		n-Pr	H	Cl	H	isobutyl	2,5-furanyl
572		i-Pr	H	Cl	H	isobutyl	2,5-furanyl
573		acetyl	H	Cl	H	isobutyl	2,5-furanyl
574		carboxy	H	Cl	H	isobutyl	2,5-furanyl
575		carboxy-amido	H	Cl	H	isobutyl	2,5-furanyl
576		SH	H	Cl	H	isobutyl	2,5-furanyl

577		-NHNH2	H	Cl	H	isobutyl	2,5-furanyl
578		-NHOH	H	Cl	H	isobutyl	2,5-furanyl
579		H	Et	Cl	H	isobutyl	2,5-furanyl
580		H	CN	Cl	H	isobutyl	2,5-furanyl
581		H	CO2H	Cl	H	isobutyl	2,5-furanyl
582		H	CO2NH2	Cl	H	isobutyl	2,5-furanyl
583		H	H	Me	H	isobutyl	2,5-furanyl
584		H	H	acetenyl	H	isobutyl	2,5-furanyl
585		H	H	ethynyl	H	isobutyl	2,5-furanyl
586		H	H	ethyl	H	isobutyl	2,5-furanyl
587		H	H	NO2	H	isobutyl	2,5-furanyl
588		H	H	NH2	H	isobutyl	2,5-furanyl
589		H	H	CN	H	isobutyl	2,5-furanyl
590		H	H	SMe	H	isobutyl	2,5-furanyl
591		H	H	OMe	H	isobutyl	2,5-furanyl
592		H	H	phenyl	H	isobutyl	2,5-furanyl
593		H	H	Cl	H	m-OHPh	2,5-furanyl
594		H	H	Cl	H	p-OHPh	2,5-furanyl
595		H	H	Cl	H	m-CO2HPh	2,5-furanyl
596		H	H	Cl	H	p-CO2HPh	2,5-furanyl
597		H	H	Cl	H	m-CONH2Ph	2,5-furanyl
598		H	H	Cl	H	p-CO2HPh	2,5-furanyl
599		H	H	Cl	H	m-ClPh	2,5-furanyl
600		H	H	Cl	H	p-ClPh	2,5-furanyl
601		H	H	Cl	H	COCH2CH3	2,5-furanyl
602		H	H	Cl	H	COPh	2,5-furanyl
603		H	H	Cl	H	SO2CH3	2,5-furanyl
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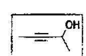
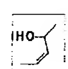
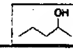
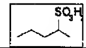
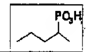
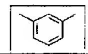
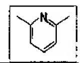
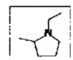
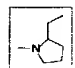
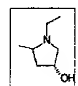
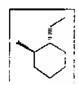
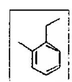
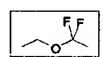
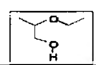
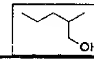
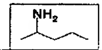
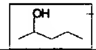
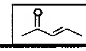
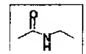
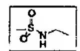
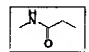
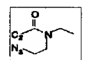
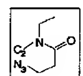
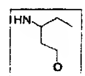
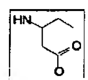
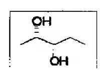
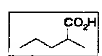
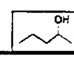
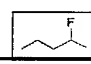
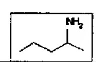
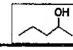
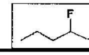
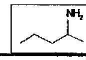
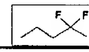
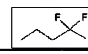
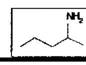
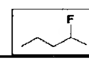
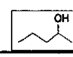
605		H	H	Cl	H	isobutyl	
606		H	H	Cl	H	isobutyl	

607		H	H	Cl	H	isobutyl	
608		H	H	Cl	H	isobutyl	
609		H	H	Cl	H	isobutyl	
610		H	H	Cl	H	isobutyl	
611		H	H	Cl	H	isobutyl	
612		H	H	Cl	H	isobutyl	
613		H	H	Cl	H	isobutyl	
614		H	H	Cl	H	isobutyl	
615		H	H	Cl	H	isobutyl	
616		H	H	Cl	H	isobutyl	
617		H	H	Cl	H	isobutyl	
618		H	H	Cl	H	isobutyl	

619		H	H	Cl	H	isobutyl	
620		H	H	Cl	H	isobutyl	
621		H	H	Cl	H	isobutyl	
622		H	H	Cl	H	isobutyl	
623		H	H	Cl	H	isobutyl	
624		H	H	Cl	H	isobutyl	
625		H	H	Cl	H	isobutyl	
626		H	H	Cl	H	isobutyl	
627		H	H	Cl	H	isobutyl	
628		H	H	Cl	H	isobutyl	
629		H	H	Cl	H	isobutyl	
630		H	H	Cl	H	isobutyl	
631		H	H	Cl	H	isobutyl	

632	13.63	H	Cl	Me	Me	isobutyl	2,5-furanyl
633	13.60	Me	Me	Cl	H	isobutyl	2,5-furanyl
634	13.58	H	H	Cl	H	cyclopropylmethyl	2,5-furanyl
635		Me	Me	H	H	isobutyl	2,5-furanyl
636	13.56	H	H	Cl	H	neopentyl	2,5-furanyl
637		Cl	H	Cl	H	neopentyl	2,5-furanyl
638		H	F	H	Et	isobutyl	2,5-furanyl
639		H	F	SMe	Et	isobutyl	2,5-furanyl
640		H	F	Cl	Et	isobutyl	2,5-furanyl
641		H	F	Br	Et	isobutyl	2,5-furanyl
642		H	F	Cl	Br	isobutyl	2,5-furanyl
643		H	H	Cl	H	neopentyl	2,5-furanyl
644		H	F	F	H	H	2,5-furanyl
645		NH2	F	H	2,6-difluorophenyl	isobutyl	methoxymethyl
646		NH2	F	H	Br	isobutyl	methoxymethyl
647		NH2	F	H	H	isobutyl	methoxymethyl
648		NH2	F	H	Et	isobutyl	methoxymethyl
649		NH2	F	H	Cl	isobutyl	methoxymethyl
650		NH2	F	H	Me	isobutyl	methoxymethyl
651		NH2	F	H	Pr	isobutyl	methoxymethyl
652		NH2	F	H	i-Pr	isobutyl	methoxymethyl
653		NH2	F	H	Bu	isobutyl	methoxymethyl
654		NH2	F	H	i-Bu	isobutyl	methoxymethyl
655		NH2	F	H	OMe	isobutyl	methoxymethyl
656		NH2	F	H	OEt	isobutyl	methoxymethyl
657		NH2	F	H	SMe	isobutyl	methoxymethyl
658		NH2	F	H	SEt	isobutyl	methoxymethyl
659		NH2	F	H	NEt2	isobutyl	methoxymethyl
660		NH2	F	H	NMe2	isobutyl	methoxymethyl
661		NH2	F	H	I	isobutyl	methoxymethyl
662		NH2	F	H	m-OMePhenyl	isobutyl	methoxymethyl
663		NH2	F	H	o-OMePhenyl	isobutyl	methoxymethyl
664		NH2	F	H	p-F Phenyl	isobutyl	methoxymethyl
665		NH2	F	H	o-F Phenyl	isobutyl	methoxymethyl

666		NH2	F	H	m-F Phenyl	isobutyl	methoxymethyl
667		NH2	F	H	2-Furanyl	isobutyl	methoxymethyl
668		NH2	F	H	2-thiophenyl	isobutyl	methoxymethyl
669		NH2	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
670		NH2	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
671		NH2	F	H	CN	isobutyl	methoxymethyl
672		NH2	F	H	m-Cl phenyl	isobutyl	methoxymethyl
673		NH2	F	H	p-Cl phenyl	isobutyl	methoxymethyl
674		NH2	F	H	o-Cl phenyl	isobutyl	methoxymethyl
675		NH2	F	H	m-Br Phenyl	isobutyl	methoxymethyl
676		NH2	F	H	p-Br Phenyl	isobutyl	methoxymethyl
677		NH2	F	H	o-Br Phenyl	isobutyl	methoxymethyl
678		NH2	F	H	CF3	isobutyl	methoxymethyl
679		NH2	F	H	cyclopentyl	isobutyl	methoxymethyl
680		NH2	F	H	cyclohexyl	isobutyl	methoxymethyl
681		NH2	F	H	cyclobutyl	isobutyl	methoxymethyl
682		NH2	F	H	cyclopropyl	isobutyl	methoxymethyl
683		NH2	F	H	Phenyl	isobutyl	methoxymethyl
684		NH2	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
685		NH2	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
686		NH2	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
687		NH2	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
688		NH2	F	H	Et	neopentyl	2,5-furanyl
689		NH2	F	H	Et	Ph	2,5-furanyl
690		NH2	F	H	Et	isobutyl	
691		NH2	F	H	Et	isobutyl	
692		NH2	F	H	Et	isobutyl	
693		NH2	F	H	Et	isobutyl	

694		NH2	F	H	Et	isobutyl	CONHCH2
695		NH2	F	H	Et	isobutyl	NHCOCH2
696		NH2	F	Cl	Et	isobutyl	
697		NH2	F	Cl	Et	isobutyl	
698		NH2	F	Cl	Et	isobutyl	
699		NH2	F	Cl	Et	isobutyl	
700		NH2	F	Cl	Et	isobutyl	CONHCH2
701		NH2	F	Cl	Et	isobutyl	NHCOCH2
702	13.4	H	$-(CH_2)_3-$		H	isobutyl	2,5-furanyl
703	13.3	H	$-(CH_2)_3-$		H	H	2,5-furanyl
704		H	H		$-(CH_2)_3-$	1,7-cyclohexyl	2,5-furanyl
705		Me	Me	Cl	Et	cyclopropylmethyl	2,5-furanyl
706		Me	Me	Cl	Cl	cyclopropylmethyl	2,5-furanyl
707		Me	Me	Cl	H	cyclopropylmethyl	methoxymethyl
708		Me	Me	Cl	H	cyclopropylmethyl	
709		Me	Me	Cl	H	cyclopropylmethyl	
710		Me	Me	Cl	H	cyclopropylmethyl	
711		Me	Me	Cl	H	cyclopropylmethyl	
712		Me	Me	Cl	H	cyclopropylmethyl	NHCOCH2
713		Me	Me	Cl	H	cyclopropylmethyl	CONHCH2
714		Me	Me	Cl	H	Ph	2,5-furanyl
715		Me	Me	Cl	H	cyclobutylmethyl	2,5-furanyl
716		Me	Me	Cl	F	cyclopropylmethyl	2,5-furanyl

717		Me	Me	Cl	Pr	cyclopropylmethyl	2,5-furanyl
718		Me	Me	Cl	Bu	cyclopropylmethyl	2,5-furanyl
719		Me	Me	Cl	OMe	cyclopropylmethyl	2,5-furanyl
720		Me	Me	Cl	OEt	cyclopropylmethyl	2,5-furanyl
721		Me	Me	Cl	i-Pr	cyclopropylmethyl	2,5-furanyl
722		Me	Me	SMe	H	cyclopropylmethyl	2,5-furanyl
723		Me	Me	F	H	cyclopropylmethyl	2,5-furanyl
724		Me	Me	Me	H	cyclopropylmethyl	2,5-furanyl
725		Cl	Cl	Cl	H	cyclopropylmethyl	2,5-furanyl
726		Me	Cl	Cl	H	cyclopropylmethyl	2,5-furanyl
727		Cl	Me	Cl	H	cyclopropylmethyl	2,5-furanyl
728		Cl	Cl	Me	H	cyclopropylmethyl	2,5-furanyl
729	12.7	NH2	H	H	H	isobutyl	2,5-furanyl
730	12.41	NH2	H	H	H	3-thienylmethyl	2,5-furanyl
731	12.43	NH2	H	H	H	1-hydroxypropyl-3-yl	2,5-furanyl
732	13.34	H	F	F	H	isobutyl	2,5-furanyl
733	13.55	H	H	H	Me	neopentyl	2,5-furanyl
734	13.57	H	Cl	H	H	cyclopropylmethyl	2,5-furanyl
735	13.61	Me	Me	Cl	H	cyclopropylmethyl	2,5-furanyl
736	13.62	H	H	Me	Me	isobutyl	2,5-furanyl
737	13.64	H	F	H	Br	isobutyl	2,5-furanyl
738	13.65	H	H	Cl	H	3-methoxyphenyl	2,5-furanyl
739	13.66	H	H	H	H	H	-C(O)NHCH2-
740		Me	F	H	Br	isobutyl	2,5-furanyl
741		Me	F	H	H	isobutyl	2,5-furanyl
742		Me	F	H	Et	isobutyl	2,5-furanyl
743		Me	F	H	Cl	isobutyl	2,5-furanyl
744		Me	F	H	Me	isobutyl	2,5-furanyl
745		Me	F	H	Pr	isobutyl	2,5-furanyl
746		Me	F	H	I-Pr	isobutyl	2,5-furanyl
747		Me	F	H	Bu	isobutyl	2,5-furanyl
748		Me	F	H	i-Bu	isobutyl	2,5-furanyl
749		Me	F	H	OMe	isobutyl	2,5-furanyl

750		Me	F	H	OEt	isobutyl	2,5-furanyl
751		Me	F	H	SMe	isobutyl	2,5-furanyl
752		Me	F	H	SEt	isobutyl	2,5-furanyl
753		Me	F	H	NEt2	isobutyl	2,5-furanyl
754		Me	F	H	NMe2	isobutyl	2,5-furanyl
755		Me	F	H	I	isobutyl	2,5-furanyl
756		Me	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
757		Me	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
758		Me	F	H	p-F Phenyl	isobutyl	2,5-furanyl
759		Me	F	H	o-F Phenyl	isobutyl	2,5-furanyl
760		Me	F	H	m-F Phenyl	isobutyl	2,5-furanyl
761		Me	F	H	2-Furanyl	isobutyl	2,5-furanyl
762		Me	F	H	2-thiophenyl	isobutyl	2,5-furanyl
763		Me	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
764		Me	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
765		Me	F	H	CN	isobutyl	2,5-furanyl
766		Me	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
767		Me	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
768		Me	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
769		Me	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
770		Me	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
771		Me	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
773		Me	F	H	CF3	isobutyl	2,5-furanyl
774		Me	F	H	cyclopentyl	isobutyl	2,5-furanyl
775		Me	F	H	cyclohexyl	isobutyl	2,5-furanyl
776		Me	F	H	cyclobutyl	isobutyl	2,5-furanyl
777		Me	F	H	cyclopropyl	isobutyl	2,5-furanyl
778		Me	F	H	Phenyl	isobutyl	2,5-furanyl
779		Me	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
780		Me	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
781		Me	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
782		Me	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
783		H	F	H	Br	isobutyl	2,5-furanyl
784		H	F	H	H	isobutyl	2,5-furanyl

785		H	F	H	Et	isobutyl	2,5-furanyl
786		H	F	H	Cl	isobutyl	2,5-furanyl
787		H	F	H	Me	isobutyl	2,5-furanyl
788		H	F	H	Pr	isobutyl	2,5-furanyl
789		H	F	H	i-Pr	isobutyl	2,5-furanyl
790		H	F	H	Bu	isobutyl	2,5-furanyl
791		H	F	H	i-Bu	isobutyl	2,5-furanyl
792		H	F	H	OMe	isobutyl	2,5-furanyl
793		H	F	H	OEt	isobutyl	2,5-furanyl
794		H	F	H	SMe	isobutyl	2,5-furanyl
795		H	F	H	SEt	isobutyl	2,5-furanyl
796		H	F	H	NEt2	isobutyl	2,5-furanyl
797		H	F	H	NMe2	isobutyl	2,5-furanyl
798		H	F	H	I	isobutyl	2,5-furanyl
799		H	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
800		H	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
801		H	F	H	p-F Phenyl	isobutyl	2,5-furanyl
802		H	F	H	o-F Phenyl	isobutyl	2,5-furanyl
803		H	F	H	m-F Phenyl	isobutyl	2,5-furanyl
804		H	F	H	2-Furanyl	isobutyl	2,5-furanyl
805		H	F	H	2-thiophenyl	isobutyl	2,5-furanyl
806		H	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
807		H	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
808		H	F	H	CN	isobutyl	2,5-furanyl
809		H	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
810		H	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
811		H	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
812		H	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
813		H	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
814		H	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
815		H	F	H	CF3	isobutyl	2,5-furanyl
816		H	F	H	cyclopentyl	isobutyl	2,5-furanyl
817		H	F	H	cyclohexyl	isobutyl	2,5-furanyl
818		H	F	H	cyclobutyl	isobutyl	2,5-furanyl

819		H	F	H	cyclopropyl	isobutyl	2,5-furanyl
820		H	F	H	Phenyl	isobutyl	2,5-furanyl
821		H	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
822		H	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
823		H	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
824		H	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
825		Cl	F	H	Br	isobutyl	2,5-furanyl
826		Cl	F	H	H	isobutyl	2,5-furanyl
827		Cl	F	H	Et	isobutyl	2,5-furanyl
828		Cl	F	H	Cl	isobutyl	2,5-furanyl
829		Cl	F	H	Me	isobutyl	2,5-furanyl
830		Cl	F	H	Pr	isobutyl	2,5-furanyl
831		Cl	F	H	i-Pr	isobutyl	2,5-furanyl
832		Cl	F	H	Bu	isobutyl	2,5-furanyl
833		Cl	F	H	i-Bu	isobutyl	2,5-furanyl
834		Cl	F	H	OMe	isobutyl	2,5-furanyl
835		Cl	F	H	OEt	isobutyl	2,5-furanyl
836		Cl	F	H	SMe	isobutyl	2,5-furanyl
837		Cl	F	H	SEt	isobutyl	2,5-furanyl
838		Cl	F	H	NEt2	isobutyl	2,5-furanyl
839		Cl	F	H	NMe2	isobutyl	2,5-furanyl
840		Cl	F	H	I	isobutyl	2,5-furanyl
841		Cl	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
842		Cl	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
843		Cl	F	H	p-F Phenyl	isobutyl	2,5-furanyl
844		Cl	F	H	o-F Phenyl	isobutyl	2,5-furanyl
845		Cl	F	H	m-F Phenyl	isobutyl	2,5-furanyl
846		Cl	F	H	2-Furanyl	isobutyl	2,5-furanyl
847		Cl	F	H	2-thiophenyl	isobutyl	2,5-furanyl
848		Cl	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
849		Cl	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
850		Cl	F	H	CN	isobutyl	2,5-furanyl
851		Cl	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
852		Cl	F	H	p-Cl phenyl	isobutyl	2,5-furanyl

853		Cl	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
854		Cl	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
855		Cl	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
856		Cl	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
857		Cl	F	H	CF3	isobutyl	2,5-furanyl
858		Cl	F	H	cyclopentyl	isobutyl	2,5-furanyl
859		Cl	F	H	cyclohexyl	isobutyl	2,5-furanyl
860		Cl	F	H	cyclobutyl	isobutyl	2,5-furanyl
861		Cl	F	H	cyclopropyl	isobutyl	2,5-furanyl
862		Cl	F	H	Phenyl	isobutyl	2,5-furanyl
863		Cl	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
864		Cl	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
865		Cl	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
866		Cl	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
867		Cl	F	H	Br	isobutyl	methoxymethyl
868		Cl	F	H	H	isobutyl	methoxymethyl
869		Cl	F	H	Et	isobutyl	methoxymethyl
870		Cl	F	H	Cl	isobutyl	methoxymethyl
871		Cl	F	H	Me	isobutyl	methoxymethyl
872		Cl	F	H	Pr	isobutyl	methoxymethyl
873		Cl	F	H	i-Pr	isobutyl	methoxymethyl
874		Cl	F	H	Bu	isobutyl	methoxymethyl
875		Cl	F	H	i-Bu	isobutyl	methoxymethyl
876		Cl	F	H	OMe	isobutyl	methoxymethyl
877		Cl	F	H	OEt	isobutyl	methoxymethyl
878		Cl	F	H	SMe	isobutyl	methoxymethyl
879		Cl	F	H	SEt	isobutyl	methoxymethyl
880		Cl	F	H	NEt2	isobutyl	methoxymethyl
881		Cl	F	H	NMe2	isobutyl	methoxymethyl
882		Cl	F	H	I	isobutyl	methoxymethyl
883		Cl	F	H	m-OMePhenyl	isobutyl	methoxymethyl
884		Cl	F	H	o-OMePhenyl	isobutyl	methoxymethyl
885		Cl	F	H	p-F Phenyl	isobutyl	methoxymethyl
886		Cl	F	H	o-F Phenyl	isobutyl	methoxymethyl

887		Cl	F	H	m-F Phenyl	isobutyl	methoxymethyl
888		Cl	F	H	2-Furanyl	isobutyl	methoxymethyl
889		Cl	F	H	2-thiophenyl	isobutyl	methoxymethyl
890		Cl	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
891		Cl	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
892		Cl	F	H	CN	isobutyl	methoxymethyl
893		Cl	F	H	m-Cl phenyl	isobutyl	methoxymethyl
894		Cl	F	H	p-Cl phenyl	isobutyl	methoxymethyl
895		Cl	F	H	o-Cl phenyl	isobutyl	methoxymethyl
896		Cl	F	H	m-Br Phenyl	isobutyl	methoxymethyl
897		Cl	F	H	p-Br Phenyl	isobutyl	methoxymethyl
898		Cl	F	H	o-Br Phenyl	isobutyl	methoxymethyl
899		Cl	F	H	CF3	isobutyl	methoxymethyl
900		Cl	F	H	cyclopentyl	isobutyl	methoxymethyl
901		Cl	F	H	cyclohexyl	isobutyl	methoxymethyl
902		Cl	F	H	cyclobutyl	isobutyl	methoxymethyl
903		Cl	F	H	cyclopropyl	isobutyl	methoxymethyl
904		Cl	F	H	Phenyl	isobutyl	methoxymethyl
905		Cl	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
906		Cl	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
907		Cl	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
908		Cl	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
909		H	F	H	Br	isobutyl	methoxymethyl
910		H	F	H	H	isobutyl	methoxymethyl
911		H	F	H	Et	isobutyl	methoxymethyl
912		H	F	H	Cl	isobutyl	methoxymethyl
913		H	F	H	Me	isobutyl	methoxymethyl
914		H	F	H	Pr	isobutyl	methoxymethyl
915		H	F	H	i-Pr	isobutyl	methoxymethyl
916		H	F	H	Bu	isobutyl	methoxymethyl
917		H	F	H	i-Bu	isobutyl	methoxymethyl
918		H	F	H	OMe	isobutyl	methoxymethyl
919		H	F	H	OEt	isobutyl	methoxymethyl
920		H	F	H	SMe	isobutyl	methoxymethyl

921		H	F	H	SEt	isobutyl	methoxymethyl
922		H	F	H	NEt2	isobutyl	methoxymethyl
923		H	F	H	NMe2	isobutyl	methoxymethyl
924		H	F	H	I	isobutyl	methoxymethyl
925		H	F	H	m-OMePhenyl	isobutyl	methoxymethyl
926		H	F	H	o-OMePhenyl	isobutyl	methoxymethyl
927		H	F	H	p-F Phenyl	isobutyl	methoxymethyl
928		H	F	H	o-F Phenyl	isobutyl	methoxymethyl
929		H	F	H	m-F Phenyl	isobutyl	methoxymethyl
930		H	F	H	2-Furanyl	isobutyl	methoxymethyl
931		H	F	H	2-thiophenyl	isobutyl	methoxymethyl
932		H	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
933		H	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
934		H	F	H	CN	isobutyl	methoxymethyl
935		H	F	H	m-Cl phenyl	isobutyl	methoxymethyl
936		H	F	H	p-Cl phenyl	isobutyl	methoxymethyl
937		H	F	H	o-Cl phenyl	isobutyl	methoxymethyl
938		H	F	H	m-Br Phenyl	isobutyl	methoxymethyl
939		H	F	H	p-Br Phenyl	isobutyl	methoxymethyl
940		H	F	H	o-Br Phenyl	isobutyl	methoxymethyl
941		H	F	H	CF3	isobutyl	methoxymethyl
942		H	F	H	cyclopentyl	isobutyl	methoxymethyl
943		H	F	H	cyclohexyl	isobutyl	methoxymethyl
944		H	F	H	cyclobutyl	isobutyl	methoxymethyl
945		H	F	H	cyclopropyl	isobutyl	methoxymethyl
946		H	F	H	Phenyl	isobutyl	methoxymethyl
947		H	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
948		H	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
949		H	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
950		H	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
951		Me	F	H	Br	isobutyl	methoxymethyl
952		Me	F	H	H	isobutyl	methoxymethyl
953		Me	F	H	Et	isobutyl	methoxymethyl
954		Me	F	H	Cl	isobutyl	methoxymethyl

955		Me	F	H	Me	isobutyl	methoxymethyl
956		Me	F	H	Pr	isobutyl	methoxymethyl
957		Me	F	H	i-Pr	isobutyl	methoxymethyl
958		Me	F	H	Bu	isobutyl	methoxymethyl
959		Me	F	H	i-Bu	isobutyl	methoxymethyl
960		Me	F	H	OMe	isobutyl	methoxymethyl
961		Me	F	H	OEt	isobutyl	methoxymethyl
962		Me	F	H	SMe	isobutyl	methoxymethyl
963		Me	F	H	SEt	isobutyl	methoxymethyl
964		Me	F	H	NEt2	isobutyl	methoxymethyl
965		Me	F	H	NMe2	isobutyl	methoxymethyl
966		Me	F	H	I	isobutyl	methoxymethyl
967		Me	F	H	m-OMePhenyl	isobutyl	methoxymethyl
968		Me	F	H	o-OMePhenyl	isobutyl	methoxymethyl
969		Me	F	H	p-F Phenyl	isobutyl	methoxymethyl
970		Me	F	H	o-F Phenyl	isobutyl	methoxymethyl
971		Me	F	H	m-F Phenyl	isobutyl	methoxymethyl
972		Me	F	H	2-Furanyl	isobutyl	methoxymethyl
973		Me	F	H	2-thiophenyl	isobutyl	methoxymethyl
974		Me	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
975		Me	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
976		Me	F	H	CN	isobutyl	methoxymethyl
977		Me	F	H	m-Cl phenyl	isobutyl	methoxymethyl
978		Me	F	H	p-Cl phenyl	isobutyl	methoxymethyl
979		Me	F	H	o-Cl phenyl	isobutyl	methoxymethyl
980		Me	F	H	m-Br Phenyl	isobutyl	methoxymethyl
981		Me	F	H	p-Br Phenyl	isobutyl	methoxymethyl
982		Me	F	H	o-Br Phenyl	isobutyl	methoxymethyl
983		Me	F	H	CF3	isobutyl	methoxymethyl
984		Me	F	H	cyclopentyl	isobutyl	methoxymethyl
985		Me	F	H	cyclohexyl	isobutyl	methoxymethyl
986		Me	F	H	cyclobutyl	isobutyl	methoxymethyl
987		Me	F	H	cyclopropyl	isobutyl	methoxymethyl
988		Me	F	H	Phenyl	isobutyl	methoxymethyl

989		Me	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
990		Me	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
991		Me	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
992		Me	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
993		Me	F	H	Br	isobutyl	CONHCH2
994		Me	F	H	H	isobutyl	CONHCH2
995		Me	F	H	Et	isobutyl	CONHCH2
996		Me	F	H	Cl	isobutyl	CONHCH2
997		Me	F	H	Me	isobutyl	CONHCH2
998		Me	F	H	Pr	isobutyl	CONHCH2
999		Me	F	H	i-Pr	isobutyl	CONHCH2
1000		Me	F	H	Bu	isobutyl	CONHCH2
1001		Me	F	H	i-Bu	isobutyl	CONHCH2
1002		Me	F	H	OMe	isobutyl	CONHCH2
1003		Me	F	H	OEt	isobutyl	CONHCH2
1004		Me	F	H	SMe	isobutyl	CONHCH2
1005		Me	F	H	SEt	isobutyl	CONHCH2
1006		Me	F	H	NEt2	isobutyl	CONHCH2
1007		Me	F	H	NMe2	isobutyl	CONHCH2
1008		Me	F	H	I	isobutyl	CONHCH2
1009		Me	F	H	m-OMePhenyl	isobutyl	CONHCH2
1010		Me	F	H	o-OMePhenyl	isobutyl	CONHCH2
1011		Me	F	H	p-F Phenyl	isobutyl	CONHCH2
1012		Me	F	H	o-F Phenyl	isobutyl	CONHCH2
1013		Me	F	H	m-F Phenyl	isobutyl	CONHCH2
1014		Me	F	H	2-Furanyl	isobutyl	CONHCH2
1015		Me	F	H	2-thiophenyl	isobutyl	CONHCH2
1016		Me	F	H	2-Furanylmethyl	isobutyl	CONHCH2
1017		Me	F	H	2-Thiophenylmethyl	isobutyl	CONHCH2
1018		Me	F	H	CN	isobutyl	CONHCH2
1019		Me	F	H	m-Cl phenyl	isobutyl	CONHCH2
1020		Me	F	H	p-Cl phenyl	isobutyl	CONHCH2
1021		Me	F	H	o-Cl phenyl	isobutyl	CONHCH2
1022		Me	F	H	m-Br Phenyl	isobutyl	CONHCH2

1023		Me	F	H	p-Br Phenyl	isobutyl	CONHCH2
1024		Me	F	H	o-Br Phenyl	isobutyl	CONHCH2
1025		Me	F	H	CF3	isobutyl	CONHCH2
1026		Me	F	H	cyclopentyl	isobutyl	CONHCH2
1027		Me	F	H	cyclohexyl	isobutyl	CONHCH2
1028		Me	F	H	cyclobutyl	isobutyl	CONHCH2
1029		Me	F	H	cyclopropyl	isobutyl	CONHCH2
1030		Me	F	H	Phenyl	isobutyl	CONHCH2
1031		Me	F	H	cyclopentylmethyl	isobutyl	CONHCH2
1032		Me	F	H	cyclohexylmethyl	isobutyl	CONHCH2
1033		Me	F	H	cyclobutylmethyl	isobutyl	CONHCH2
1034		Me	F	H	cyclopropylmethyl	isobutyl	CONHCH2
1035		H	F	H	Br	isobutyl	CONHCH2
1036		H	F	H	H	isobutyl	CONHCH2
1037		H	F	H	Et	isobutyl	CONHCH2
1038		H	F	H	Cl	isobutyl	CONHCH2
1039		H	F	H	Me	isobutyl	CONHCH2
1040		H	F	H	Pr	isobutyl	CONHCH2
1041		H	F	H	i-Pr	isobutyl	CONHCH2
1042		H	F	H	Bu	isobutyl	CONHCH2
1043		H	F	H	i-Bu	isobutyl	CONHCH2
1044		H	F	H	OMe	isobutyl	CONHCH2
1045		H	F	H	OEt	isobutyl	CONHCH2
1046		H	F	H	SMe	isobutyl	CONHCH2
1047		H	F	H	SEt	isobutyl	CONHCH2
1048		H	F	H	NEt2	isobutyl	CONHCH2
1049		H	F	H	NMe2	isobutyl	CONHCH2
1050		H	F	H	I	isobutyl	CONHCH2
1051		H	F	H	m-OMePhenyl	isobutyl	CONHCH2
1052		H	F	H	o-OMePhenyl	isobutyl	CONHCH2
1053		H	F	H	p-F Phenyl	isobutyl	CONHCH2
1054		H	F	H	o-F Phenyl	isobutyl	CONHCH2
1055		H	F	H	m-F Phenyl	isobutyl	CONHCH2
1056		H	F	H	2-Furanyl	isobutyl	CONHCH2

1057		H	F	H	2-thiophenyl	isobutyl	CONHCH2
1058		H	F	H	2-Furanylmethyl	isobutyl	CONHCH2
1059		H	F	H	2-Thiophenylmethyl	isobutyl	CONHCH2
1060		H	F	H	CN	isobutyl	CONHCH2
1061		H	F	H	m-Cl phenyl	isobutyl	CONHCH2
1062		H	F	H	p-Cl phenyl	isobutyl	CONHCH2
1063		H	F	H	o-Cl phenyl	isobutyl	CONHCH2
1064		H	F	H	m-Br Phenyl	isobutyl	CONHCH2
1065		H	F	H	p-Br Phenyl	isobutyl	CONHCH2
1066		H	F	H	o-Br Phenyl	isobutyl	CONHCH2
1067		H	F	H	CF3	isobutyl	CONHCH2
1068		H	F	H	cyclopentyl	isobutyl	CONHCH2
1069		H	F	H	cyclohexyl	isobutyl	CONHCH2
1070		H	F	H	cyclobutyl	isobutyl	CONHCH2
1071		H	F	H	cyclopropyl	isobutyl	CONHCH2
1072		H	F	H	Phenyl	isobutyl	CONHCH2
1073		H	F	H	cyclopentylmethyl	isobutyl	CONHCH2
1074		H	F	H	cyclohexylmethyl	isobutyl	CONHCH2
1075		H	F	H	cyclobutylmethyl	isobutyl	CONHCH2
1076		H	F	H	cyclopropylmethyl	isobutyl	CONHCH2
1077		Cl	F	H	Br	isobutyl	CONHCH2
1078		Cl	F	H	H	isobutyl	CONHCH2
1079		Cl	F	H	Et	isobutyl	CONHCH2
1080		Cl	F	H	Cl	isobutyl	CONHCH2
1081		Cl	F	H	Me	isobutyl	CONHCH2
1082		Cl	F	H	Pr	isobutyl	CONHCH2
1083		Cl	F	H	i-Pr	isobutyl	CONHCH2
1084		Cl	F	H	Bu	isobutyl	CONHCH2
1085		Cl	F	H	i-Bu	isobutyl	CONHCH2
1086		Cl	F	H	OMe	isobutyl	CONHCH2
1087		Cl	F	H	OEt	isobutyl	CONHCH2
1088		Cl	F	H	SMe	isobutyl	CONHCH2
1089		Cl	F	H	SEt	isobutyl	CONHCH2
1090		Cl	F	H	NEt2	isobutyl	CONHCH2

1091		Cl	F	H	NMe2	isobutyl	CONHCH2
1092		Cl	F	H	I	isobutyl	CONHCH2
1093		Cl	F	H	m-OMePhenyl	isobutyl	CONHCH2
1094		Cl	F	H	o-OMePhenyl	isobutyl	CONHCH2
1095		Cl	F	H	p-F Phenyl	isobutyl	CONHCH2
1096		Cl	F	H	o-F Phenyl	isobutyl	CONHCH2
1097		Cl	F	H	m-F Phenyl	isobutyl	CONHCH2
1098		Cl	F	H	2-Furanyl	isobutyl	CONHCH2
1099		Cl	F	H	2-thiophenyl	isobutyl	CONHCH2
1100		Cl	F	H	2-Furanylmethyl	isobutyl	CONHCH2
1101		Cl	F	H	2-Thiophenylmethyl	isobutyl	CONHCH2
1102		Cl	F	H	CN	isobutyl	CONHCH2
1103		Cl	F	H	m-Cl phenyl	isobutyl	CONHCH2
1104		Cl	F	H	p-Cl phenyl	isobutyl	CONHCH2
1105		Cl	F	H	o-Cl phenyl	isobutyl	CONHCH2
1106		Cl	F	H	m-Br Phenyl	isobutyl	CONHCH2
1107		Cl	F	H	p-Br Phenyl	isobutyl	CONHCH2
1108		Cl	F	H	o-Br Phenyl	isobutyl	CONHCH2
1109		Cl	F	H	CF3	isobutyl	CONHCH2
1110		Cl	F	H	cyclopentyl	isobutyl	CONHCH2
1111		Cl	F	H	cyclohexyl	isobutyl	CONHCH2
1112		Cl	F	H	cyclobutyl	isobutyl	CONHCH2
1113		Cl	F	H	cyclopropyl	isobutyl	CONHCH2
1114		Cl	F	H	Phenyl	isobutyl	CONHCH2
1115		Cl	F	H	cyclopentylmethyl	isobutyl	CONHCH2
1116		Cl	F	H	cyclohexylmethyl	isobutyl	CONHCH2
1117		Cl	F	H	cyclobutylmethyl	isobutyl	CONHCH2
1118		Cl	F	H	cyclopropylmethyl	isobutyl	CONHCH2
1119		Me	F	H	Br	isobutyl	NHCOCH2
1120		Me	F	H	H	isobutyl	NHCOCH2
1121		Me	F	H	Et	isobutyl	NHCOCH2
1122		Me	F	H	Cl	isobutyl	NHCOCH2
1123		Me	F	H	Me	isobutyl	NHCOCH2
1124		Me	F	H	Pr	isobutyl	NHCOCH2

1125		Me	F	H	i-Pr	isobutyl	NHCOCH2
1126		Me	F	H	Bu	isobutyl	NHCOCH2
1127		Me	F	H	i-Bu	isobutyl	NHCOCH2
1128		Me	F	H	OMe	isobutyl	NHCOCH2
1129		Me	F	H	OEt	isobutyl	NHCOCH2
1130		Me	F	H	SMe	isobutyl	NHCOCH2
1131		Me	F	H	SEt	isobutyl	NHCOCH2
1132		Me	F	H	NEt2	isobutyl	NHCOCH2
1133		Me	F	H	NMe2	isobutyl	NHCOCH2
1134		Me	F	H	I	isobutyl	NHCOCH2
1135		Me	F	H	m-OMePhenyl	isobutyl	NHCOCH2
1136		Me	F	H	o-OMePhenyl	isobutyl	NHCOCH2
1137		Me	F	H	p-F Phenyl	isobutyl	NHCOCH2
1138		Me	F	H	o-F Phenyl	isobutyl	NHCOCH2
1139		Me	F	H	m-F Phenyl	isobutyl	NHCOCH2
1140		Me	F	H	2-Furanyl	isobutyl	NHCOCH2
1141		Me	F	H	2-thiophenyl	isobutyl	NHCOCH2
1142		Me	F	H	2-Furanylmethyl	isobutyl	NHCOCH2
1143		Me	F	H	2-Thiophenylmethyl	isobutyl	NHCOCH2
1144		Me	F	H	CN	isobutyl	NHCOCH2
1145		Me	F	H	m-Cl phenyl	isobutyl	NHCOCH2
1146		Me	F	H	p-Cl phenyl	isobutyl	NHCOCH2
1147		Me	F	H	o-Cl phenyl	isobutyl	NHCOCH2
1148		Me	F	H	m-Br Phenyl	isobutyl	NHCOCH2
1149		Me	F	H	p-Br Phenyl	isobutyl	NHCOCH2
1150		Me	F	H	o-Br Phenyl	isobutyl	NHCOCH2
1151		Me	F	H	CF3	isobutyl	NHCOCH2
1152		Me	F	H	cyclopentyl	isobutyl	NHCOCH2
1153		Me	F	H	cyclohexyl	isobutyl	NHCOCH2
1154		Me	F	H	cyclobutyl	isobutyl	NHCOCH2
1155		Me	F	H	cyclopropyl	isobutyl	NHCOCH2
1156		Me	F	H	Phenyl	isobutyl	NHCOCH2
1157		Me	F	H	cyclopentylmethyl	isobutyl	NHCOCH2
1158		Me	F	H	cyclohexylmethyl	isobutyl	NHCOCH2

1159		Me	F	H	cyclobutylmethyl	isobutyl	NHCOCH2
1160		Me	F	H	cyclopropylmethyl	isobutyl	NHCOCH2
1161		H	F	H	Br	isobutyl	NHCOCH2
1162		H	F	H	H	isobutyl	NHCOCH2
1163		H	F	H	Et	isobutyl	NHCOCH2
1164		H	F	H	Cl	isobutyl	NHCOCH2
1165		H	F	H	Me	isobutyl	NHCOCH2
1166		H	F	H	Pr	isobutyl	NHCOCH2
1167		H	F	H	i-Pr	isobutyl	NHCOCH2
1168		H	F	H	Bu	isobutyl	NHCOCH2
1169		H	F	H	i-Bu	isobutyl	NHCOCH2
1170		H	F	H	OMe	isobutyl	NHCOCH2
1171		H	F	H	OEt	isobutyl	NHCOCH2
1172		H	F	H	SMe	isobutyl	NHCOCH2
1173		H	F	H	SEt	isobutyl	NHCOCH2
1174		H	F	H	NEt2	isobutyl	NHCOCH2
1175		H	F	H	NMe2	isobutyl	NHCOCH2
1176		H	F	H	I	isobutyl	NHCOCH2
1177		H	F	H	m-OMePhenyl	isobutyl	NHCOCH2
1178		H	F	H	o-OMePhenyl	isobutyl	NHCOCH2
1179		H	F	H	p-F Phenyl	isobutyl	NHCOCH2
1180		H	F	H	o-F Phenyl	isobutyl	NHCOCH2
1181		H	F	H	m-F Phenyl	isobutyl	NHCOCH2
1182		H	F	H	2-Furanyl	isobutyl	NHCOCH2
1183		H	F	H	2-thiophenyl	isobutyl	NHCOCH2
1184		H	F	H	2-Furanylmethyl	isobutyl	NHCOCH2
1185		H	F	H	2-Thiophenylmethyl	isobutyl	NHCOCH2
1186		H	F	H	CN	isobutyl	NHCOCH2
1187		H	F	H	m-Cl phenyl	isobutyl	NHCOCH2
1188		H	F	H	p-Cl phenyl	isobutyl	NHCOCH2
1189		H	F	H	o-Cl phenyl	isobutyl	NHCOCH2
1190		H	F	H	m-Br Phenyl	isobutyl	NHCOCH2
1191		H	F	H	p-Br Phenyl	isobutyl	NHCOCH2
1192		H	F	H	o-Br Phenyl	isobutyl	NHCOCH2

1193		H	F	H	CF3	isobutyl	NHCOCH2
1194		H	F	H	cyclopentyl	isobutyl	NHCOCH2
1195		H	F	H	cyclohexyl	isobutyl	NHCOCH2
1196		H	F	H	cyclobutyl	isobutyl	NHCOCH2
1197		H	F	H	cyclopropyl	isobutyl	NHCOCH2
1198		H	F	H	Phenyl	isobutyl	NHCOCH2
1199		H	F	H	cyclopentylmethyl	isobutyl	NHCOCH2
1200		H	F	H	cyclohexylmethyl	isobutyl	NHCOCH2
1201		H	F	H	cyclobutylmethyl	isobutyl	NHCOCH2
1202		H	F	H	cyclopropylmethyl	isobutyl	NHCOCH2
1203		Cl	F	H	Br	isobutyl	NHCOCH2
1204		Cl	F	H	H	isobutyl	NHCOCH2
1205		Cl	F	H	Et	isobutyl	NHCOCH2
1206		Cl	F	H	Cl	isobutyl	NHCOCH2
1207		Cl	F	H	Me	isobutyl	NHCOCH2
1208		Cl	F	H	Pr	isobutyl	NHCOCH2
1209		Cl	F	H	i-Pr	isobutyl	NHCOCH2
1210		Cl	F	H	Bu	isobutyl	NHCOCH2
1211		Cl	F	H	i-Bu	isobutyl	NHCOCH2
1212		Cl	F	H	OMe	isobutyl	NHCOCH2
1213		Cl	F	H	OEt	isobutyl	NHCOCH2
1214		Cl	F	H	SMe	isobutyl	NHCOCH2
1215		Cl	F	H	SEt	isobutyl	NHCOCH2
1216		Cl	F	H	NEt2	isobutyl	NHCOCH2
1217		Cl	F	H	NMe2	isobutyl	NHCOCH2
1218		Cl	F	H	I	isobutyl	NHCOCH2
1219		Cl	F	H	m-OMePhenyl	isobutyl	NHCOCH2
1220		Cl	F	H	o-OMePhenyl	isobutyl	NHCOCH2
1221		Cl	F	H	p-F Phenyl	isobutyl	NHCOCH2
1222		Cl	F	H	o-F Phenyl	isobutyl	NHCOCH2
1223		Cl	F	H	m-F Phenyl	isobutyl	NHCOCH2
1224		Cl	F	H	2-Furanyl	isobutyl	NHCOCH2
1225		Cl	F	H	2-thiophenyl	isobutyl	NHCOCH2
1226		Cl	F	H	2-Furanylmethyl	isobutyl	NHCOCH2

1227		Cl	F	H	2-Thiophenylmethyl	isobutyl	NHCOCH2
1228		Cl	F	H	CN	isobutyl	NHCOCH2
1229		Cl	F	H	m-Cl phenyl	isobutyl	NHCOCH2
1230		Cl	F	H	p-Cl phenyl	isobutyl	NHCOCH2
1231		Cl	F	H	o-Cl phenyl	isobutyl	NHCOCH2
1232		Cl	F	H	m-Br Phenyl	isobutyl	NHCOCH2
1233		Cl	F	H	p-Br Phenyl	isobutyl	NHCOCH2
1234		Cl	F	H	o-Br Phenyl	isobutyl	NHCOCH2
1235		Cl	F	H	CF3	isobutyl	NHCOCH2
1236		Cl	F	H	cyclopentyl	isobutyl	NHCOCH2
1237		Cl	F	H	cyclohexyl	isobutyl	NHCOCH2
1238		Cl	F	H	cyclobutyl	isobutyl	NHCOCH2
1239		Cl	F	H	cyclopropyl	isobutyl	NHCOCH2
1240		Cl	F	H	Phenyl	isobutyl	NHCOCH2
1241		Cl	F	H	cyclopentylmethyl	isobutyl	NHCOCH2
1242		Cl	F	H	cyclohexylmethyl	isobutyl	NHCOCH2
1243		Cl	F	H	cyclobutylmethyl	isobutyl	NHCOCH2
1244		Cl	F	H	cyclopropylmethyl	isobutyl	NHCOCH2
1245		Me	Me	Cl	H	isobutyl	2,5-furanyl
1246	13.62	H	H	Me	Me	isobutyl	2,5-furanyl
1247	13.63	H	Cl	Me	Me	isobutyl	2,5-furanyl
1248	13.67	H	F	H	Br	isobutyl	2,5-furanyl
1249	13.68	H	F	NO_2	Br	isobutyl	2,5-furanyl
1250	13.69	H	F	NH_2	Br	isobutyl	2,5-furanyl
1251	13.70	NH_2	Cl	Me	Me	isobutyl	2,5-furanyl
1252	12.66	NH_2	F	H	cyclopropyl	isobutyl	2,5-furanyl
1253	12.67	NH_2	F	H	phenyl	isobutyl	2,5-furanyl
1254	12.68	NH_2	F	H	*p*-F-phenyl	isobutyl	2,5-furanyl
1255	12.69	NH_2	F	H	*p*-Cl-Phenyl	isobutyl	2,5-furanyl
1256	12.70	NH_2	F	H	vinyl	isobutyl	2,5-furanyl
1257	13.71	H	F	NMe_2	F	isobutyl	2,5-furanyl
1258	13.72	H	H	H	CH_2OH	isobutyl	2,5-furanyl
1259	12.71	NH_2	F	H	4-Me-pentyl	isobutyl	2,5-furanyl
1260	13.73	H	F	H	Br	H	2,5-furanyl

1261	13.74	NO_2	F	H	Br	H	2,5-furanyl
1262	13.75	H	F	NO_2	Br	H	2,5-furanyl
1263	12.73	NH_2	F	H	H	2-Et-butyl	2,5-furanyl
1264	12.72	NH_2	F	H	3,3-diMe-butyl	isobutyl	2,5-furanyl
1265	12.74	NH_2	F	H	*m*-OMe-phenyl	isobutyl	2,5-furanyl
1266	13.77	NHCO Me	F	H	Et	isobutyl	2,5-furanyl
1267	13.76	H	F	NHCO Me	Br	isobutyl	2,5-furanyl
1268	12.75	NH_2	F	H	Et	cyclopropylmethyl	2,5-furanyl
1269	12.76	NH_2	F	H	H	3-pentyl	2,5-furanyl
1270	13.79	H	F	NMe_2	Br	isobutyl	2,5-furanyl
1271	13.78	NMe_2	F	H	Et	isobutyl	2,5-furanyl
1272	12.77	H	F	F	F	isobutyl	2,5-furanyl
1273	12.78	F	F	F	H	isobutyl	2,5-furanyl
1274	13.80	H	F	Cl	Et	H	2,5-furanyl
1275	13.81	Et	Cl	F	H	isobutyl	2,5-furanyl
1276	13.83	Me	Me	Me	Me	isobutyl	2,5-furanyl
1277	13.82	Me	Me	Me	Me	H	2,5-furanyl
1278	12.79	NH_2	F	H	3-OH-propyl	isobutyl	2,5-furanyl
1279	13.86	H	H	H	H	H	$CONHCHCO_2$ Me
1280	13.84	Me	H	Me	H	H	2,5-furanyl
1281	13.85	Me	H	Me	H	isobutyl	2,5-furanyl
1282	13.87	H	Me	H	Me	isobutyl	2,5-furanyl
1283	12.80	NH_2	F	H	3-Br-propyl	isobutyl	2,5-furanyl
1284	12.81	NH_2	F	H	propyl	isobutyl	2,5-furanyl
1285	12.82	NH_2	F	H	4-Br-butyl	isobutyl	2,5-furanyl
1286	12.83	NH_2	F	H	4-Cl-butyl	isobutyl	2,5-furanyl
1287	13.88	Me	Me	Me	Me	cyclopropylmethyl	2,5-furanyl
1288	13.89	Me	Me	Cl	H	ethyl	2,5-furanyl
1289	13.90	Me	Me	Cl	H	4-Br-butyl	2,5-furanyl
1290	12.85	Me	Me	Cl	H	cyclopropylmethyl	2,5-thionyl
1291	13.91	Me	Me	Cl	Br	H	2,5-furanyl

1292	13.92	Me	Me	Cl	Br	isobutyl	2,5-furanyl
1293	15.1	NH_2	F	H	Br	isobutyl	methoxymethyl
1294	12.84	NH_2	F	H	3-*(N,N*-dimethyl)propylamine	isobutyl	2,5-furanyl
1295	13.96	Br	Cl	Me	Me	isobutyl	2,5-furanyl
1296	13.94	H	Cl	H	H	*n*-butylamine	2,5-furanyl
1297	13.95	H	H	Cl	H	*n*-butylamine	2,5-furanyl
1298	13.96	Me	Cl	H	H	isobutyl	2,5-furanyl
1299		H	Me	Cl	H	isobutyl	2,5-furanyl
1300		Cl	Me	Cl	H	isobutyl	2,5-furanyl
1301		NH_2	F	H	Et	isobutyl	methoxymethyl
1302		NH_2	F	H	4-bromobutyl	isobutyl	methoxymethyl
1303		NH_2	F	H	3-bromopropyl	isobutyl	methoxymethyl
1304		NH_2	F	H	4-chlorobutyl	isobutyl	methoxymethyl
1305		NH_2	F	H	3-chloropropyl	isobutyl	methoxymethyl
1306		NH_2	F	H	3-hydroxypropyl	isobutyl	methoxymethyl
1307		NH_2	F	H	4-hydroxybutyl	isobutyl	methoxymethyl
1308		NH_2	F	H	3-*(N,N*-dimethyl)propylamine	isobutyl	methoxymethyl
1309	17.1	H	H	H	H	H	$-CONHCH_2-$
1310		NH_2	F	H	H	isobutyl	methoxymetthyl
1311	12.86	NH_2	F	H	Et	H	2,5-furanyl

More preferred are the following compounds from Table 1 and salts and prodrugs thereof:

41, 42, 43, 53, 55, 56, 57, 58, 59, 60, 62, 63, 87, 88, 128, 281, 282, 322, 354, 484, 485, 490, 491, 494, 504, 506, 568, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 654, 696, 697, 698, 699, 700, 701, 705, 706, 707, 708, 709, 710, 1248, 1249, 1251, 1252, 1253, 1254, 1255, 1256, 1259, 1263, 1264, 1265, 1268, 1269, 1273, 1276, 1277, 1278, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1293, 1294, 1295, 1298.

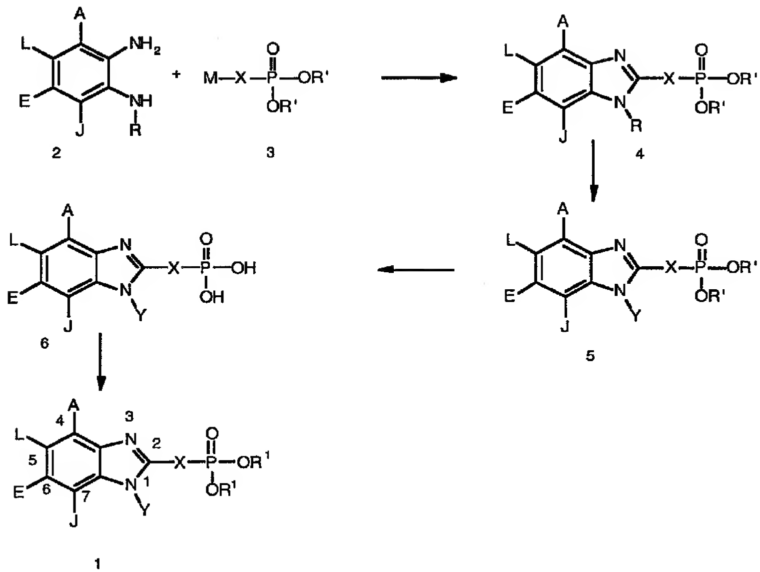
Most preferred are the following compounds from Table 1 and salts and prodrugs thereof:

5-Fluoro-7-bromo-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4,5-Dimethyl-6-chloro-1-isopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole;
6-Chloro-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole;
5,6-Difluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4-Amino-5,7-dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4-Amino-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4-Amino-5-fluoro-7-chloro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-6-chloro-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-6-methylthio-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-6-chloro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
1-isobutyl-4-methyl-5-chloro-2(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-isobutylbenzimidazol-2-ylmethyleneoxymethylphosphonic acid;
4-Amino-5,6-difluoro-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-neopentyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-cyclobutylmethyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(1-hydroxy-1-phosphonopropyl)benzimidazole; and
4-Amino-5-fluoro-7-isopropyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-cyclopropyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-phenyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-(4-methylpentyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-(3-hydroxypropyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-(3-bromopropyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-(4-bromobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-(4-chlorobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-(3-N,N-dimethylpropylamine)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.
4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(1-methoxymethyl-3-phosphono)benzimidazole.
4-Amino-5-fluoro-1-isobutyl-2-(1-methoxymethyl-3-phosphono)benzimidazole.

<u>Synthesis of Compounds of Formula 1</u>

Synthesis of the compounds encompassed by the present invention typically includes some or all of the following general steps: (1) synthesis of the prodrug ; (2) phosphonate deprotection; (3) substitution of the heterocycle; (4) substitution or modification of 2-substituent; (5) cyclization to generate benzimidazole ring system; (6) synthesis of the linker-PO_3R_2; and (7) synthesis of the substituted 1,2-phenylenediamine. A detailed discussion of each step is given below.



1) Preparation of Phosphonate Prodrugs

Prodrug esters can be introduced at different stages of the synthesis. Most often, these prodrugs are made from the phosphonic acids of formula 6 because of their lability. Advantageously, these prodrug esters can be introduced at an earlier stage, provided they can withstand the reaction conditions of the subsequent steps.

Compounds of formula 6, can be alkylated with electrophiles (such as alkyl halides, alkyl sulfonates, etc) under nucleophilic substitution reaction conditions to give phosphonate esters. For example, prodrugs of formula 1, where R^1 is acyloxymethyl group can be synthesized through direct alkylation of the free phosphonic acid of formula 6 with the desired acyloxymethyl halide (e.g. $Me_3CC(O)OCH_2I$; Elhaddadi, et al *Phosphorus Sulfur*, **1990**, *54(1-4)*: 143; Hoffmann, *Synthesis*, **1988**, 62) in presence of base e.g. *N, N'*-dicyclohexyl-4-morpholinecarboxamidine, Hunigs base, etc. in polar aprotic solvents such as DMF (Starrett, et al, *J. Med. Chem.*, **1994**, 1857). These carboxylates include but are not limited to acetate, propionate, isobutyrate, pivalate, benzoate, and

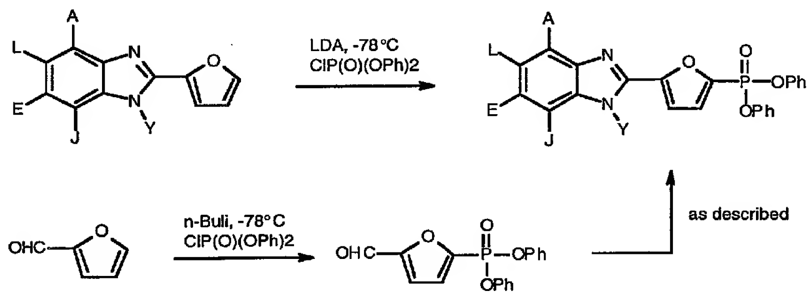
other carboxylates. Alternately, these acyloxymethylphosphonate esters can also be synthesized by treatment of the nitrophosphonic acid (A is NO_2 in formula 6; Dickson, et al, *J. Med. Chem.*, **1996**, *39*: 661; Iyer, et al, *Tetrahedron Lett.*, **1989**, *30*: 7141; Srivastva, et al, *Bioorg. Chem.*, **1984**, *12*: 118). This methodology can be extended to many other types of prodrugs, such as compounds of formula 1 where R1 is 3-phthalidyl, 2-oxo-4,5-didehydro-1,3-dioxolanemethyl, and 2-oxotetrahydrofuran-5-yl groups, etc. (Biller and Magnin (US 5,157,027); Serafinowska et al. (J. Med. Chem. *38*: 1372 (1995)); Starrett et al. (J. Med. Chem. *37*: 1857 (1994)); Martin et al. J. Pharm. Sci. *76*: 180 (1987); Alexander et al., Collect. Czech. Chem. Commun, *59*: 1853 (1994)); and EPO 0632048A1). *N,N*-Dimethylformamide dialkyl acetals can also be used to alkylate phosphonic acids (Alexander, P., et al *Collect. Czech. Chem. Commun.*, **1994**, *59*, 1853).

Alternatively, these phosphonate prodrugs or phosphoramidates can also be synthesized, by reaction of the corresponding dichlorophosphonate and an alcohol or an amine (Alexander, et al, *Collect. Czech. Chem. Commun.*, **1994**, *59*: 1853). For example, the reaction of dichlorophosphonate with phenols and benzyl alcohols in the presence of base (such as pyridine, triethylamine, etc) yields compounds of formula 1 where R^1 is aryl (Khamnei, S., et al *J. Med. Chem.*, **1996**, *39*: 4109; Serafinowska, H.T., et al *J. Med. Chem.*, **1995**, *38*: 1372; De Lombaert, S., et al *J. Med. Chem.*, **1994**, *37*: 498) or benzyl (Mitchell, A.G., et al *J. Chem. Soc. Perkin Trans. 1*, **1992**, *38*: 2345). The disulfide-containing prodrugs, reported by Puech et al., *Antiviral Res.*, **1993**, *22*: 155, can also be prepared from dichlorophosphonate and 2-hydroxyethyl disulfide under standard conditions.

Such reactive dichlorophosphonate intermediates, can be prepared from the corresponding phosphonic acids and chlorinating agents e.g. thionyl chloride (Starrett, et al, *J. Med. Chem.*, **1994**, 1857), oxalyl chloride (Stowell, et al, *Tetrahedron Lett.*, **1990**, *31*: 3261), and phosphorus pentachloride (Quast, et al, *Synthesis*, **1974**, 490). Alternatively, these dichlorophosphonates can also be generated from disilylphosphonate esters (Bhongle, et al, *Synth. Commun.*, **1987**, *17*: 1071) and dialkylphosphonate esters (Still, et al, *Tetrahedron Lett.*, **1983**, *24*: 4405; Patois, et al, *Bull. Soc. Chim. Fr.*, **1993**, *130*: 485).

Furthermore, these prodrugs can be prepared from Mitsunobu reactions (Mitsunobu, *Synthesis*, **1981**, 1; Campbell, *J.Org. Chem.*, **1992**, *52*: 6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, *Collect. Czech. Chem. Commun.*, **1994**, *59*: 1853; Casara, et al, *Bioorg. Med. Chem. Lett.*, **1992**, *2*: 145; Ohashi, et al, *Tetrahedron Lett.*, **1988**, *29*: 1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, et al, *Tetrahedron Lett.*, **1993**, *34*: 6743). The prodrugs of formula 1 where R^1 is the cyclic carbonate or lactone or phthalidyl can also be synthesized by direct alkylation of free phosphonic acid with the desired halides in the presence of base such as NaH or diisopropylethylamine (Biller and Magnin US 5,157,027; Serafinowska et al. J. Med. Chem. *38*: 1372 (1995); Starrett et al. J. Med. Chem. *37*: 1857 (1994); Martin et al. *J. Pharm. Sci. 76*: 180 (1987); Alexander et al., Collect. Czech. Chem. Commun, *59*: 1853 (1994); and EPO 0632048A1).

R^1 can also be introduced at an early stage of the synthesis. For example, compounds of formula 1 where R^1 is phenyl can be prepared by phosphorylation of 2-furanyl benzimidazole subjected to a strong base (e.g. LDA) and chlorodiphenyl phosphonate. Alternatively, such compounds can be prepared by alkylation of lithiated furfuraldehyde followed by ring closure to the benzimidazole.



It is envisioned that compounds of formula 1 can be mixed phosphonate esters (e.g. phenyl benzyl phosphonate esters, phenyl acyloxyalkyl phosphonate esters, etc). For example, the chemically combined phenyl-benzyl prodrugs are reported by Meier, et al. *Bioorg. Med. Chem. Lett.*, **1997**, *7*: 99.

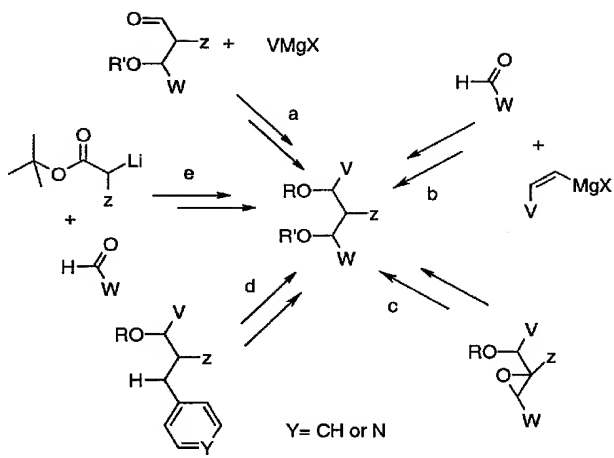
The substituted cyclic propyl phosphonate esters of formula **1**, can be synthesized by reaction of the corresponding dichlorophosphonate and the substituted 1,3-propane diol. The following are some methods to prepare the substituted 1,3-propane diols.

Synthesis of the 1,3-Propane Diols Used in the Preparation of Certain Prodrugs

The discussion of this step includes various synthetic methods for the preparation of the following types of propane-1,3-diols: i) 1-substituted; ii) 2-substituted; and iii) 1,2- or 1,3-annulated. Different groups on the prodrug part of the molecule *i.e.*, on the propane diol moiety can be introduced or modified either during the synthesis of the diols or after the synthesis of the prodrugs.

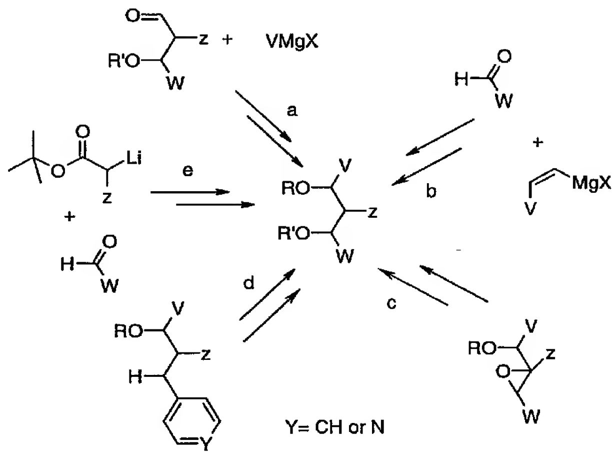
i) 1-Substituted 1,3-Propane Diols

Propane-1,3-diols can be synthesized by several well known methods in the literature. Aryl Grignard additions to 1-hydroxypropan-3-al gives 1-aryl-substituted propane-1,3-diols (path a). This method will enable conversion of various substituted aryl halides to 1-arylsubstituted-1,3-propane diols (Coppi, et. al., *J. Org. Chem.*, **1988**, *53*, 911). Aryl halides can also be used to synthesize 1-substituted propanediols by Heck coupling of 1,3-diox-4-ene followed by reduction and hydrolysis (Sakamoto, et. al., *Tetrahedron Lett.*, **1992**, *33*, 6845). A variety of aromatic aldehydes can be converted to 1-substituted-1,3-propane diols by vinyl Grignard addition followed by hydroboration (path b). Substituted aromatic aldehydes are also useful for lithium-t-butylacetate addition followed by ester reduction (path e) (Turner., *J. Org. Chem.*, **1990**, *55* 4744). In another method, commercially available cinnamyl alcohols can be converted to epoxy alcohols under catalytic asymmetric epoxidation conditions. These epoxy alcohols are reduced by Red-Al to result in enantiomerically pure propane-1,3-diols (path c). Alternatively, enantiomerically pure 1,3-diols can be obtained by chiral borane reduction of hydroxyethyl aryl ketone derivatives (Ramachandran, et. al., *Tetrahedron Lett.*, **1997**, *38* 761). Pyridyl, quinoline, and isoquinoline propan-3-ol derivatives can be oxygenated to 1-substituted propan-1,3-diols by N-oxide formation followed by rearrangement under acetic anhydride conditions (path d) (Yamamoto, et. al., *Tetrahedron* , **1981**, *37*, 1871).



ii) 2-Substituted 1,3-Propane Diols:

Various 2-substituted propane-1,3-diols can be made from commercially available 2-(hydroxymethyl)-1,3-propane diol. Triethyl methanetricarboxylate can be converted to the triol by complete reduction (path a) or diol-monocarboxylic acid derivatives can be obtained by partial hydrolysis and diester reduction (Larock, *Comprehensive Organic Transformations*, VCH, New York, **1989**). Nitrotriol is also known to give the triol by reductive elimination (path b) (Latour, et. al., *Synthesis*, **1987**, *8*, 742). The triol can be derivatized as a mono acetate or carbonate by treatment with alkanoyl chloride, or alkylchloroformate, respectively (path d) (Greene and Wuts, *Protective Groups in Organic Synthesis*, John Wiley, New York, **1990**). Aryl substitution effected by oxidation to the aldehyde followed by aryl Grignard additions (path c) and the aldehyde can also be converted to substituted amines by reductive amination reactions (path e).



iii) Annulated 1,3-Propane Diols:

Prodrugs of formula 1 where V - Z or V - W are fused by three carbons are made from cyclohexane diol derivatives. Commercially available *cis, cis*-1,3,5-cyclohexane triol can be used for prodrug formation. This cyclohexanetriol can also be modified as described in the case of 2-substituted propan-1,3-diols to give various analogues. These modifications can either be made before or after formation of prodrugs. Various 1,3-cyclohexane diols can be made by Diels-Alder methodology using pyrone as the diene (Posner, et. al., *Tetrahedron Lett.*, **1991**, *32,* 5295). Cyclohexyl diol derivatives are also made by nitrile oxide olefin-additions (Curran, et. al., *J. Am. Chem. Soc.,* **1985**, *107,* 6023). Alternatively, cyclohexyl precursors can be made from quinic acid (Rao, et. al., *Tetrahedron Lett.*, **1991**, *32,* 547.)

2) Phosphonate Deprotection

Compounds of formula 6, may be prepared from phosphonate esters of formula 5, using known phosphate and phosphonate ester cleavage conditions. In general, silyl halides have been used to cleave the various phosphonate esters, followed by mild hydrolysis of the resulting silyl phosphonate esters to give the desired phosphonic acids. Depending on the stability of the products,

these reactions are usually accomplished in the presence of acid scavengers such as 1,1,1,3,3,3-hexamethyldisilazane, 2,6-lutidine, etc. Such silyl halides include, chlorotrimethylsilane (Rabinowitz, *J. Org. Chem.*, **1963**, *28*: 2975), bromotrimethylsilane (McKenna, et al, *Tetrahedron Lett.*, **1977**, 155), iodotrimethylsilane (Blackburn, et al, *J. Chem. Soc., Chem. Commun.*, **1978**, 870). Alternately, phosphonate esters can be cleaved under strong acid conditions, (e.g HBr, HCl, etc.) in polar solvents, preferably acetic acid (Moffatt, et al, *U.S. Patent 3,524,846*, **1970**) or water. These esters can also be cleaved via dichlorophosphonates, prepared by treating the esters with with halogenating agents e.g. phosphorus pentachloride, thionyl chloride, BBr_3, etc.(Pelchowicz, et al, *J. Chem. Soc.*, **1961**, 238) followed by aqueous hydrolysis to give phosphonic acids. Aryl and benzyl phosphonate esters can be cleaved under hydrogenolysis conditions (Lejczak, et al, *Synthesis*, **1982**, 412; Elliott, et al, *J. Med. Chem.*, **1985**, *28*: 1208; Baddiley, et al, *Nature*, **1953**, *171*: 76) or dissolving metal reduction conditions(Shafer, et al, *J. Am. Chem. Soc.*, **1977**, *99*: 5118). Electrochemical (Shono, et al, *J. Org. Chem.*, **1979**, *44*: 4508) and pyrolysis (Gupta, et al, *Synth. Commun.*, **1980**, *10*: 299) conditions have also been used to cleave various phosphonate esters.

<u>3) Substitution of the Heterocycle</u>

The benzimidazole ring system of formula 4, may require further elaboration to provide desired compounds of formula 5.

<u>i) Substitution of the Phenyl Ring</u>

Electrophilic and nucleophilic substitution reactions enable incorporation of the desired substitutions encompassed by the formula 5. (March, *Advanced Organic Chemistry* by, Wiley-Interscience, **1992**, 501-521; 641-654). For example, treatment of the compounds of formula 4 , where A is NH_2, L and J are hydrogens with NBS, NCS or NIS in halogenated solvents such as carbon tetrachloride or chloroform gives halo-substituted compounds of formula 5 (L and/or J are halogens). Compounds of formula 5, where A is NO_2, L and/or J are alkenyl, alkynyl, alkyl, or aryl groups, and Y is H or alkyl, may be prepared from compounds of formula 4, where A is NO_2, R is H or alkyl, and L and/or J are halogens, preferably bromide or iodide, through Stille coupling (Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*: 508-524). Treatment of the compounds of formula 4, where A is NO_2, and L and/or J are bromides, with a coupling reagent (e.g. tributyl(vinyl)tin, phenylboronic acid, propargyl alcohol, *N,N*-propargyl

amine etc.) in presence of palladium catalyst [e.g. bis(triphenylphosphine)palladium (II)chloride, tetrakis(triphenylphosphine) palladium(0), etc.] in solvent, such as DMF, toluene, etc. provides the coupling products. The compounds thus obtained can be modified as needed. For example vinyl or propargyl alcohol derivatives can be hydrogenated to give the ethyl or propyl alcohol derivatives respectively. These alcohols can be further modified as required *via* alkyl halides (ref. Wagner et al. *Tetrahedron Lett.* **1989**, *30,* 557.) or alkyl sulfonates etc. to a number of substituted alkyls such as amino alkyl compounds by subjecting them to nucleophilic substitution reactions (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 293-500). Alternatively, these substitutions can also be done by metal exchange followed by quenching with an appropriate nucleophile (Jerry March, *Advanced Organic Chemistry* , Wiley-Interscience, **1992**, 606-609). Nucleophilic addition reactions can also be useful in preparing compounds of formula 5. For example, when A is NO_2, L and/or J are halogens, nucleophiles such as alkoxides, thiols, amines, etc. provide the halogen displacement products. (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 649-676). Another example is addition reactions, for example cyclopropanation (Vorbruggen et al, *Tetrahedron Lett.* **1975**, 629), on the olefins(e.g. styryl type) synthesized through Stille coupling.

If required, these substituted compounds can be further modified to the desired products. For example, reduction of the NO_2 to NH_2 may be done in many different ways, e.g. Pd/C, H_2, aq. $Na_2S_2O_4$, etc. (Larock, *Comprehensive Organic Transformations* , VCH, 412-415). These primary aromatic amines can also be modified as needed. For example, N-acetyl derivatives can be prepared by treatment with acetyl chloride or acetic anhydride in the presence of a base such as pyridine. The mono- or di-alkylamines can be synthesized by direct alkylation, using a base such as NaH in polar solvents such as DMF or by reductive alkylation methods (ref. Abdel-Magid et al. *Tetrahedron Lett.* **1990**, *31*, 5595; also see ref. March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 898-900 for more methods).

ii) Alkylation of the Imidazole Ring

Alkylation of the heterocycle of formula 4, (where R and J are both H) is obtained through two distinct methods that are amenable to a large number of electrophiles: a) Mitsunobu alkylation, and b) base alkylation.

a) Mitsunobu Alkylation

Alkylation of the benzimidazole ring system of formula 4, is achieved by treatment of an alcohol, triphenylphosphine and dialkylazodicarboxylate with heterocycle and a non-nucleophilic base such as Hunigs base in polar solvents such as CH_3CN (Zwierzak et al, *Liebigs Ann. Chem.* **1986**, 402).

b) Base Alkylation

Alternately, the benzimidazole ring system of formula 4 can be deprotonated with a suitable base, preferably cesium carbonate in a polar aprotic solvent such as DMF, and the resulting anion is alkylated with an appropriate electrophilic component Y-L', where L' is a leaving group preferably bromide or iodide.

4) Substitution or Modification of a 2-substituent

Another key intermediate envisioned in the synthesis of compounds of formula 4 are substituted 2-methylbenzimidazoles. These compounds are readily prepared by condensing Ac_2O with the appropriate 1,2-phenylenediamine (Phillips, *J. Chem. Soc.,* **1928**, *29*: 1305). These compounds are useful in the synthesis of formula 1, wherein X is CH_2ZCH_2(Z=O,S,NH). For example, compounds where Z=O are readily prepared by treatment of the 2-methylbenzimidazole with a halogenating agent such as NBS followed by reaction with the α-hydroxy phosphonate ester (also see section 6, Synthesis of the Linker-PO_3R_2). Alternately, a heterosubstituted methyl phosphonates can also be prepared by displacement reactions on phosphonomethyl halides or sulfonates (Phillion et al, *Tetrahedron Lett.*, **1986**, *27*: 1477.) with an appropriate nucleophile e.g. 2-hydroxylmethylbenzimidazole compound which can be prepared using a variety of methods, including oxidation of the substituted 2-methylbenzimidazoles.

Similarly, compounds of formula 1, where X is carboxypropyl or sulfonopropyl can be prepared from the reaction of 2-(2-iodoethyl) benzimidazole and corresponding phosphonomethylcarboxylate or phosphonomethylsulfonate (Carretero et al., *Tetrahedron*, **1987**, 43, 5125) in the presence of base such as NaH in polar aprotic solvents such as DMF. The

substituted 2-(2-iodoethyl) benzimidazole can be prepared from condensation of the corresponding substituted diamine and 3-halopropanaldehyde. Also see ref. Magnin, D. R. et al. *J. Med. Chem.* **1996**, 39, 657 for the preparation of α-phosphosulfonic acids.

The componds of formula 4 where X is all carbon e.g. -$(CH_2)_3$- can be prepared by Stille coupling (Stille *Angew. Chem. Int. Ed. Engl.* **1986**, *25*: 508-524) of the dialkylphosphopropenyl tributylstanne (*J. Org. Chem.* **1993**, *58*: 6531.) and appropriate 2-bromobenzimidazole (Mistry, et al, *Tetrahedron Lett.*, **1986**, *27*: 1051).

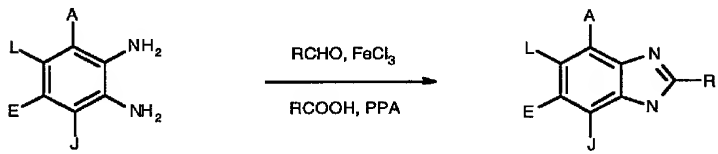
The componds of formula 4 where X is an amide linker e.g. -$CONHCH_2$- can be synthesized using the following two steps. Treatment of the appropriate 1,2-phenylenediamine with trihalomethylacetamidate preferably trichloromethylacetamidate in polar solvent such as acetic acid followed by hydrolysis of the trihalomethyl group with strong aqueous base (e.g. KOH) gives the benzimidazole-2-carboxylic acid (*Eur. J. Med. Chem.*, **1993**, *28*: 71). Condensation of the acid with an amino phosphonate e.g. diethyl(aminomethyl)phosphonate in presence of a coupling agent (e.g. pyBOP) in a polar solvent such as methylene chloride provides the amide linked phosphonate.

The componds of formula 4 where X is an amide linker e.g. -$NHCOCH_2$- can be synthesized using the following two steps. Treatment of the appropriate 1,2-phenylenediamine with cyanogenbromide (Johnson, et al, *J. Med. Chem.*, **1993**, *36*: 3361) in polar solvent such as MeOH gives the 2-amino benzimidazole. Condensation of the 2-aminobenzimidazole with a carboxylic acid e.g. diethyl(carboxymethyl)phosphonate using standard coupling conditions (Klausner, et al, *Synthesis*, **1972**, 453) provides the amide linked phosphonate. The 2-aminobenzimidazoles can also be prepared from the 2-bromobenzimidazole *via* the 2-azidobenzimidazole using known methods (*Chem. Rev.* **1988**, *88*: 297).

5) Cyclization to Generate Benzimidazole Ring System

The benzimidazole ring systems of formula 4 is preferably assembled by condensation of substituted 1,2-phenylenediamines with an aldehyde (RCHO, where R is e.g. aliphatic, heteroaliphatic, aromatic or heteroaromatic etc.) using known methods; (a) in presence of Fe^{3+} salts, preferably $FeCl_3$, in polar solvents such as DMF, EtOH etc., (b) reflux in non-polar solvents such as toluene

followed by oxidation, preferably with iodine (Bistocchi et al, *Collect. Czech. Chem. C*, **1985**, *50(9)*: 1959.)., (c) in cases of protected aldehydes, the first condensation can be achieved in the presence of a dilute inorganic acid, preferably 10 % H_2SO_4, in polar solvents such as THF, followed by oxidation with I_2. Alternatively, this coupling can be achieved with an anhydride (RCOOCOR), a carboxylic acid (RCOOH), with a nitrile (RCN) by methods reported by Hein, et al, *J. Am. Chem. Soc.* **1957**, *79,* 427.; and Applegate, et al, US 5,310,923; or imidates (R-C(=NH)-OEt) ref. Maryanoff, et al. *J. Med. Chem.* **1995**, *38*: 16.



Advantageously, these benzimidazole ring systems can be constructed using solid phase synthesis (ref: Phillips et al. *Tet. Lett.*, **1996**, *37*: 4887; Lee et al., *Tet. Lett*, **1998**: *35*: 201.

6) Synthesis of the Linker-PO_3R_2

Coupling of aromatic or aliphatic aldehydes, ketals or acetals of aldehydes, and acid derivatives with attached phophonate esters are particularly well suited for the synthesis of compounds of formula 1.

i) Preparation of Aryl and Heteroaryl Phosphonate Esters

Aryl functionalized phosphonate linkers can be prepared by lithiation of an aromatic ring using methods well described in literature (Gschwend, *Org. React.* **1979**, *26*, 1; Durst, *Comprehensive Carbanion Chemistry*, Vol. 5, Elsevier, New York, **1984**) followed by addition of phosphorylating agents (e.g. $ClPO_3R_2$). Phosphonate esters are also introduced by Arbuzov-Michaelis reaction of primary halides (Brill, T. B., *Chem Rev.*, **1984**, *84*: 577). Aryl halides undergo Ni^{2+} catalysed reaction with trialkylphosphites to give aryl phosphonate containing compounds (Balthazar, et al, *J. Org. Chem.*, **1980**, *45*: 5425). Aromatic triflates are known to result in phosphonates with $ClPO_3R_2$ in the presence of a palladium catalyst (Petrakis, et al, J. Am. Chem. Soc., **1987**, *109*:

2831; Lu, et al, *Synthesis*, **1987**, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin, *Tetrahedron Lett.*, **1981**, *22*: 3375; Casteel, et al, *Synthesis*, **1991**, 691). Using the same method described above, arylphosphate esters, where X is aryloxy, can also be made. N-Alkoxy aryl salts with alkali metal derivatives of dialkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore, *J. Org. Chem.*, **1970**, *35*: 4114).

In the linker phosphonate synthesis, aldehyde, ketone, or carboxylic acid functionalities can also be introduced after the phosphonate ester is formed. A lithiation reaction can be used to incorporate the aldehyde or ketone functionalities, although other methods known to generate aromatic aldehydes or ketones can be envisioned as well (e.g. Vilsmeier-Hack reaction, Reimar-Teimann reaction etc.; Pizey, *Synthetic reagents*, **1974**, *1*: **1**; Wynberg, H., et al, *Org. React.* **1982**, *28*: **1**; palladium catalyzed coupling reaction of acid halides and organotin compounds). For example, for the lithiation reaction, the lithiated aromatic ring can be treated with reagents that directly generate the aldehyde (*e.g.* DMF, HCOOR, *etc.*)(Einchorn, J., et al, *Tetrahedron Lett.*, **1986,** *27*: 1791), or the ketone (e.g. Weinreb's amide, RCOOR'). The lithiated aromatic ring can also be treated with reagents that lead to a group that is subsequently transformed into the aldehyde or ketone group using known chemistry (synthesis of aldehyde and ketone from alcohol, ester, cyano, alkene, *etc.*). It is also envisioned that the sequence of these reactions can be reversed, *i.e.* the aldehyde and ketone moieties can be incorporated first, followed by the phosphorylation reaction. The order of the reaction will depend on reaction conditions and protecting groups. Prior to the phosphorylation it is also envisioned that it may be advantageous to protect the aldehyde or ketone using well-known methods (acetal, aminal, hydrazone, ketal, etc.), and then the aldehyde or ketone is unmasked after phosphorylation. (*Protective groups in Organic Synthesis*, Greene, T. W., **1991**, Wiley, New York).

The above mentioned methods can also be extended to the heteroaryl linkers e.g. pyridine, furan, thiophene etc.

ii) Preparation of Aliphatic and Heteroaliphatic Phosphonate Esters

Compounds of formula 3, where M is CO_2R and X is alkyl can be synthesized using reactions well known in the art. Trialkyl phosphites attack lactones at the β-carbon atom, causing the alkyl-oxygen cleavage of the lactone ring, to yield alkyl(dialkylphosphono)esters. This reaction can be applied to many types of lactones such as β-lactones, γ-lactones etc. as reported by McConnell et al, *J. Am. Chem. Soc.,* **1956**, *78*, 4453. Alternatively, these type of compounds can be synthesized using the Arbuzov reaction (*Chem. Rev.* **1984**, *84*: 577). The linkers Ar(Z)alkyl phosphonates (Ar=aryl; Z=O,S etc.) can be prepared from the reaction of substituted aryls e.g. salicylaldehyde with an appropriate phosphonate electrophile [$L(CH2)_nPO_3R_2$, L is a leaving group, preferably iodine; Walsh et al, *J. Am. Chem. Soc.,* **1956**, *78*, 4455.] in the presence of a base, preferably K_2CO_3 or NaH, in a polar aprotic solvent, such as DMF or DMSO. For the preparation of α-phosphosulfonic acids see ref. Magnin, D. R. et al. *J. Med. Chem.* **1996,** *39,* 657; and ref. cited therein.

Compounds of formula 3, where M is CO_2R or CHO and X is carbonylalkyl can be synthesized from the acid chlorides (for example H(O)C-$CH_2C(O)Cl$) and $P(OEt)_3$ (*Chem. Rev.* **1984**, 84: 577). These α-ketophosphonates can be converted to the α-hydroxyphoshonates and α,α-dihalophosphonates (ref. Smyth, et al. *Tett. Lett.*, **1992**, 33, 4137). For another method of synthesizing these α,α-dihalophosphonates see the ref. Martin et al. *Tett. Lett.* **1992**, 33, 1839.

Compounds of formula 3, where X is a heteroalkyl linker e.g. -CH_2ZCH_2- where Z=O,S etc. and M is aldehyde or its protected form such as dialkyl acetal (*Protective groups in Organic Synthesis*, Greene, T. W., **1991**, Wiley, New York) can be prepared by nucleophilic substitution reactions (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 293-500) to give unsymmetrical ethers. For example linkers of formula 3, where X is alkyloxymethyl can be synthesized through direct alkylation of the hydroxymethyl phosphonate ester, with the desired alkyl halide [$L(CH_2)_nCH(OMe)_2$, L is a leaving group, preferably bromine or iodine] in the presence of a base, preferably NaH, in a polar aprotic solvent, such as DMF or DMSO. These methods can be extended to the heteroalkyl linkers e.g. -CH_2ZCH_2- where Z=S, NH etc.

7) Synthesis of the Substituted 1,2-phenylenediamine

1,2-Phenylenediamines utilized in the preparation of compounds of formula 1, can be synthesized using methods well known in the art.

(a) Compounds of formula 2, where R is H, can be synthesized from simple aromatic compounds. Most aromatic compounds may be nitrated given the wide variety of nitrating agents available(March, *Advanced Organic Chemistry*, Wiley-Interscience, **1992**, 522-525). Primary aromatic amines are often N-acetylated before nitration by treatment with acetyl chloride or acetic anhydride. Nitration of the these acetanilide derivatives using 60 % HNO_3 and H_2SO_4 (Monge et al, *J. Med. Chem.*, **1995**, *38*: 1786; Ridd *Chem. Soc. Rev.* **1991**, *20*: 149-165), followed by deprotection by strong acid (e.g. H_2SO_4, HCl, etc.), and hydrogenation (e.g. H_2, Pd/C; $Na_2S_2O_4$; etc.) of the resulting 2-nitroanilines provides the desired substituted 1,2-phenylenediamines. Similarly, substituted arylhalides (F,Cl,Br,I) can also be nitrated to provide α-halonitroaryl compounds followed by nucleophilic addition (e.g. NH_3, NH_2OH, etc) and reduction to generate the diamines.

(b) Diamines of formula 2, where A is NO_2 and R is H, can be produced using the method of Grivas et. al., *Synthesis* **1992,** 1283 and Tian et al *J. Chem. Soc. Perkin Trans* 1, **1993**, 257 and an appropriate o-nitroaniline. A variety of reactions can be used to substitute the o-nitroaniline. For example halogenation of the nitroaniline (e.g. Br_2 ,Cl_2 etc.) gives the corresponding 4,6-disubstituted or monosubstituted nitroaniline which can be further modified at a later stage. The nitro group can be reduced with number of reagents preferably sodium dithionite to provide the corresponding diamine. This diamine is then subjected to nitration conditions by first generating the 2,1,3-benzoselenadiazole with selenium dioxide followed by nitric acid. Substituted nitro-1,2-phenylenediamines are generated by treatment of the nitro-2,1,3-benzoselenadiazole with aqueous hydrogen iodide or NH_3/H_2S (Nyhammar et al, *Acta, Chem. Scand.* **1986,** *B40*: 583). Other methods to simultaneously protect the diamine are also envisioned.

(c) The componds of formula 2, where R is alkyl or aryl, can be synthesized using the method of Ohmori et al, *J. Med. Chem.* **1996,** *39*: 3971. Nucleophilic substitution of the o-halonitrobenzenes by treatment with various alkylamines followed by reduction (e.g. $Na_2S_2O_4$) of the nitro group provides the desired compounds. Alternately, the componds of formula 2, where R is H, can be

synthesized from these o-halonitrobenzenes *via* o-azidonitrobenzenes followed by reduction of the nitro group to provide the desired compound.
(d) Alternately, diamines of formula 2 where R is not H are prepared by reductive alkylation of the o-nitroanilines with various aldehydes(e.g. akyl, aryl etc.) in the presence of a reducing agent preferably $NaB(OAc)_3$ followed by reduction (e.g. $Na_2S_2O_4$; Pd/C, H_2 etc.) of the nitro group (Magid et al *Tetrahedron Lett.* **1990**, *31*: 5595).

Formulations

Compounds of the invention are administered orally in a total daily dose of about 0.1 mg/kg/dose to about 100 mg/kg/dose, preferably from about 0.3 mg/kg/dose to about 30 mg/kg/dose. The most preferred dose range is from 0.5 to 10 mg/kg (approximately 1 to 20 nmoles/kg/dose). The use of time-release preparations to control the rate of release of the active ingredient may be preferred. The dose may be administered in as many divided doses as is convenient. When other methods are used (e.g. intravenous administration), compounds are administered to the affected tissue at a rate from 0.3 to 300 nmol/kg/min, preferably from 3 to 100 nmoles/kg/min. Such rates are easily maintained when these compounds are intravenously administered as discussed below.

For the purposes of this invention, the compounds may be administered by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters. Oral administration is generally preferred.

Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in

order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to

provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain 20 to 2000 µmol (approximately 10 to 1000 mg) of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions. It is preferred that the pharmaceutical composition be prepared which provides easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion should contain from about 0.05 to about 50 µmol (approximately 0.025 to 25 mg) of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

As noted above, formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free flowing form such as a powder or granules, optionally mixed with a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropyl methylcellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach. This is particularly advantageous with the compounds of formula 1 when such compounds are susceptible to acid hydrolysis.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, or an appropriate fraction thereof, of a fructose 1,6-bisphosphatase inhibitor compound.

It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art.

Utility

FBPase inhibitors at the AMP site may be used to treat diabetes mellitus, lower blood glucose levels, and inhibit gluconeogenesis.

FBPase inhibitors at the AMP site may also be used to treat excess glycogen storage diseases. Excessive hepatic glycogen stores are found in patients with some glycogen storage diseases. Since the indirect pathway contributes significantly to glycogen synthesis (Shulman, G.I. Phys. Rev. 72:1019-1035 (1992)), inhibition of the indirect pathway (gluconeogenesis flux) is expected to decrease glycogen overproduction.

FBPase inhibitors at the AMP site may also be used to treat or prevent diseases associated with increased insulin levels. Increased insulin levels are associated with an increased risk of cardiovascular complications and atherosclerosis (Folsom, et al., Stroke, 25:66-73 (1994); Howard, G. et al., Circulation 93:1809-1817 (1996)). FBPase inhibitors are expected to decrease postprandial glucose levels by enhancing hepatic glucose uptake. This effect is postulated to occur in individuals that are non-diabetic (or pre-diabetic, i.e. without elevated HGO or fasting blood glucose levels). Increased hepatic glucose uptake will decrease insulin secretion and thereby decrease the risk of diseases or complications that arise from elevated insulin levels.

The compounds of this invention and their preparation can be understood further by the examples which illustrate some of the processes by which these compounds are prepared. These examples should not however be construed as specifically limiting the invention and variations of the invention, now known or later developed, are considered to fall within the scope of the present invention as hereinafter claimed.

EXAMPLES

Example 1.

Preparation of 2-Furaldehyde-5-diethylphosphonate

Method A:

To a solution of 25 mL (147.5 mmol) 2-furaldehyde diethyl acetal in 25 ml of THF at -78 °C, was added 96 mL (147.2 mmol) of a 1.6 M BuLi hexane solution. The solution was allowed to stir for 1 h at -78 °C and 24 mL (166.1 mmol) chlorodiethylphosphonate was added and stirred for 0.5 h. The mixture was quenched at -78 °C with a saturated NH_4Cl solution. The precipitates formed were filtered and the filtrate concentrated. The mixture was partitioned

between water and CH_2Cl_2 and separated. The organic layer was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting brown oil was treated with 80% acetic acid and heated at 90 °C for 4 h. Chromatography on silica using 75% ethyl acetate/hexanes yielded 9.1 g (39.2 mmol, 26.6%) of a clear oil.

Method B:

To a solution of 2.8 mL (13.75 mmol) TMEDA and 1.0 mL (13.75 mmol) furan in 9 mL of diethyl ether at -78 °C, was added 8.6 mL (13.75 mmol) of a 1.6 M BuLi hexane solution. The solution was allowed to stir for 0.5 hour at -78 °C and 2.19 mL (15.25 mmol) chlorodiethylphosphonate was added and stirred for 2 h. The mixture was quenched at -78 °C with a saturated sodium bicarbonate solution. The mixture was partitioned between water and CH_2Cl_2 and separated. The organic layer was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting brown oil was purified through Kugelrohr distillation yielding 1.978 g (9.696 mmol, 70.5%) of a clear oil.

To a solution of 16.01 g (78.41 mmol) 2-diethylphosphonfuran in 400 mL of tetrahydrofuran at -78 °C, was added 58.81 mL (117.62 mmol) of a 2M LDA solution. The solution was allowed to stir for 0.3 h at -78 °C and 9.67 mL (156.82 mmol) methylchloroformate was added and stirred for 0.5 h. The mixture was quenched at -78 °C with a saturated sodium bicarbonate solution. The mixture was partitioned between water and CH_2Cl_2 and separated. The organic layer was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting oil was purified by silica gel chromatography yielding 5.6 g (18.2 mmol, 31%) of a clear yellow oil.

Method C:

To a solution of 168 g (1.75 mol) 2-furaldehyde in 500 mL toluene was added 215 mL (1.75 mol) of N,N'-dimethylethylene diamine. The solution was refluxed using a Dean Stark trap to remove H_2O. After 2 hours of reflux, the solvent was removed under reduced pressure. The resulting dark mixture was vacuum distilled (3 mm Hg) and the fraction at 59-61 °C was collected yielding 247.8 g (85%) of clear, colorless oil.

A solution of 33.25 g (0.2 mol) furan-2-(N,N'-dimethylimidazolidine) and 30.2 mL (0.2 mol) tetramethylethylenediamine in 125 mL THF was cooled in a dry ice/IPA bath. A solution of 112 mL n-BuLi in hexane(0.28 mol,2.5M) was

added dropwise, maintaining temperature between -50 and -40 °C during addition. The reaction was allowed to warm to 0 °C over 30 minutes and was maintained at 0 °C for 45 minutes. The reaction was then cooled in a dry ice/IPA bath to -55 °C. This cooled solution was transferred to a solution of 34.7 mL (0.24 mol) diethylchlorophosphate in 125 mL THF and cooled in a dry ice/IPA bath over 45 minutes maintaining the reaction temperature between -50 °C and -38 °C. The reaction was stirred at room temperature overnight. The reaction mixture was evaporated under reduced pressure. Ethyl acetate and H_2O were added to the residue and the layers separated. The H_2O layer was washed with ethyl acetate. The ethyl acetate layers were combined, dried over magnesium sulfate and evaporated under reduced pressure yielding 59.6 g (98%) of a brown oil.

To a solution of 59.6 g 5-diethylphosphonofuran-2-(N,N'-dimethylimidazolidine) in 30 mL H_2O was added 11.5 mL of conc. H_2SO_4 dropwise until pH = 1 was obtained. The aqueous reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated sodium bicarbonate, dried over magnesium sulfate and evaporated to a brown oil. The brown oil was added to a silica column and was eluted with hexane/ethyl acetate. Product fractions were pooled and evaporated under reduced pressure yielding a dark yellow oil, 28.2 g (62%).

Example 2:

Preparation of 5-diethylphosphono-2-thiophenecarboxaldehyde.

Step 1.

A solution of 1.0 mmol 2-thienyl lithium in THF was treated with 1.0 mmol diethyl chlorophosphate at -78 °C for 1 h. Extraction and chromatography gave diethyl 2-thiophenephosphonate as a clear oil.

Step 2.

A solution 1.0 mmol of diethyl 2-thiophenephosphonate in tetrahydrofuran was treated with 1.12 mmol LDA at -78 °C for 20 min. 1.5 mmol methyl formate was added and the reaction was stirred for 1 hr. Extraction and chromotagraphy gave 5-diethylphosphono-2-thiophenecarboxaldehyde as a clear yellow oil.

Example 3:

General methods for the preparation of substituted 1,2-phenylenediamines

Method A:

Step 1.

Bromination of nitroanilines.

To a solution of 1.0 mmol of sustituted nitroaniline in 10 mL of $CHCl_3$ or a mixture of $CHCl_3$ and MeOH (7:1) was added a solution containing one equivalent of Br_2 in 5 mL of $CHCl_3$ over a period of 30 min. After stirring for 2 days at room temperature, extractive isolation provided the bromination product.

Step 2.

Reduction of nitroanilines

To a solution of 1.0 mmol of substituted nitroaniline in 15 mL of MeOH was added 15mL of saturated solution of sodium dithionite. Filtration followed by removal of solvent and extraction with EtOAc provided the pure diamine.

Step 3.

Preparation of 2,1,3-benzoselenadiazole.

To a solution of 1.0 mmol of substituted diamine in 3 mL of 50% aq. ethanol was added a solution of 1.0 mmol of SeO_2 in 1.5 mL of H_2O. The mixture quickly thickened to a slurry. The solid separated out, was filtered, washed with water, and dried.

Step 4.

Nitration of benzoselenadiazoles

To a cold (0 °C) suspension of 1.0 mmol of substituted 2,1,3-benzoselenadiazole was added dropwise a solution of 2.0 mmol of HNO_3 in 1 mL of H_2SO_4. The resultant suspension was stirred for 2 h at 15° C. The dark solution was poured onto ice, filtered, washed with water, and dried.

In the case of 5-fluoro-7-bromo-2,1,3-benzoselenadiazole there were two products in 2:1 ratio, major being the required compound, 4-nitro-5-fluoro-7-bromo-2,1,3-benzoselenadiazole. This was extracted with hot toluene from the byproduct, 4-nitro-5-hydroxy-7-bromo-2,1,3-benzoselenadiazole.

Step 5.

Substituted 3-nitro-1,2-phenylenediamine preparation

A mixture of 1.0 mmol of substituted 4-nitro-2,1,3-benzoselenadiazole in 3 mL of 57% HI was stirred at room temperature for 2 h. Saturated $NaHSO_3$ was

added and the mixture was neutralized with concentrated NH_3 solution. The product was extracted with $CHCl_3$ (5x10 mL) and the extracts were washed, dried, and evaporated.

Method B:

From 2-nitrohalobenzenes:

To a solution of 20 mmol of substituted 2-halonitrobenzene in 70 mL of DMF was added 35 mmol of alkyl or arylamine at 0 °C. After 0.5 h TLC (ethyl acetate/hexane 2:1) indicated the completion of reaction. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried, and evaporated to yield the displacement products.

Method C:

From 2-nitroanilines:

To a solution of 10 mmol of substituted 2-nitroaniline, 20 mmol of alkyl or arylaldehyde, and 60 mmol of acetic acid in 30 mL of 1,2-dichloroethane was added 30 mmol sodium triacetoxyborohydride at 0°C. The reaction was stirred overnight under nitrogen atmosphere and was quenched with saturated sodium bicarbonate solution. The product was extracted with EtOAc (3 x 75 mL) and the extract was washed, dried and evaporated. The residue was chromatographed on a silica gel column eluting with hexane-ethyl acetate (3:1) to yield the product.

These nitroanilines can be reduced to 1,2-phenylenediamines by the procedure given in the Example 3, Method A, Step 2.

Example 4.

Preparation of 2-substituted benzimidazole.

Method A:

Step 1.

A mixture of 1.0 mmol of sustituted 1,2-phenylenediamine and 1.0 mmol of 2-furaldehyde-5-diethylphosphonate in 10 mL of toluene was refluxed (oil bath temp. 140-150°C) for 1-16 h with a Dean Stark trap to remove water. Solvent was removed under reduced pressure and used the product for the next step without further purification.

Step 2.

A solution of 1.0 mmol of this coupled product and 1.0 mmol of I_2 in 5 mL of ethanol was stirred at room temperature for 1-16 h. Extraction and chromatography provided the title compound as an orange solid.

Method B:

To a solution of 1.0 mmol of substituted 1,2-phenylenediamine and 1.0 mmol of 2-furaldehyde-5-diethylphosphonate in 3 mL of DMF was added 0.2-2.0 mmol of $FeCl_3$ and heated for 1-7 h at 90 °C while bubbling air through the solution. Extraction and chromatography provided the condensation product as an orange solid.

Method C:

A solution of 1.0 mmol of substituted 1,2-phenylenediamine and 1.0 mmol of 2-furaldehyde-5-diethylphosphonate in 2 mL of MeOH and AcOH mixture (3:1) was stirred at room temperature for 16 h. Extraction and chromatography provided the condensation product as a solid.

Method D:

A mixture of 1.0 mmol of sustituted 1,2-phenylenediamine and 1.5 mmol of diethylphosphomethyl acetaldehyde dimethyl acetal ether in 4 mL of THF was heated at 75° C for 40 min. in presence of 0.5 mL of 10% H_2SO_4. Solvent was removed under reduced pressure and used for the next step without further purification.

A solution of 1.0 mmol of this coupled product and 1.0 mmol of I_2 in 5 mL of ethanol was stirred at room temperature for 16 h. Extraction and chromatography provided the required product.

Example 5.

General procedures for alkylation

Method A:

A suspension of 1.5 mmol cesium carbonate, 1.0 mmol of substituted benzimidazole-2-(5-diethylphosphonate)furan and 1.0 mmol of electrophile in 5 mL of dry DMF was heated at 80° C for 1-16 h. Extraction and chromatography provided the alkylation product as a yellow solid.

Method B:(Mitsunobu Reaction)

To a suspension of 2.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole, 6.0 mmol electrophile, 6.0 mmol triphenylphosphine, 5.0 mL diisopropylethylamine and 200 mg 4A molecular sieves in 10 mL of dry CH_3CN was added 12.0 mmol diethyl azodicarboxylate at

0 °C. The solution was allowed to warm to room temperature and stirred overnight. Extraction and chromatography provided the alkylation product as a yellow solid.

Example 6:

General procedures for Pd coupling:

Method A:

A mixture of 1.0 mmol of bromo substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole compound, 2.0 mmol of vinyltributyltin or allyltributyltin, and 0.1 mmol of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ in 4 mL of DMF was stirred and heated at 90° C for 1-16 h. Extraction and chromatography provided the coupled compound.

Method B:

A mixture of 1.0 mmol of bromo substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole, 2.0 mmol of propargyl alcohol or any terminal acetylenic compound, 0.1 mmol of $Pd(PPh_3)_2Cl_2$, and 0.1 mmol of CuI in 1 mL of Et_3N and 10 mL of CH_3CN was stirred and heated at 50-80° C for 1-16 h. Extraction and chromatography provided the coupled compound.

Method C:

A mixture of 1.0 mmol of bromo substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole, 5.0 mmol of substituted phenylboronic acid, 0.1 mmol of $Pd(PPh_3)_4$, 5 mL of sat. Na_2CO_3 and 2 mL of EtOH in 10 mL of diglyme was stirred and heated at 80-90° C for 1-16 h. Extraction and chromatography provided the coupled compound.

The compounds thus obtained can be modified as needed. For example vinyl or propargyl alcohol derivatives can be hydrogenated (see Example 9, Method A) to give the ethyl or propyl alcohol derivatives respectively. These alcohol can be further modified as required *via* alkyl halides (see Example 8) or alkyl sulfonates etc. to number of substituted alkyl compounds by subjecting them to nucleophilic substitution reactions (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 293-500). See Example 7 for the cyclopropanation of the vinyl derivative.

Example 7.

Cyclopropynation of the 4-nitro-7-vinyl-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole.

To a suspension of 1.0 mmol of 4-nitro-7-vinyl-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole and 0.1 mmol of $Pd(OAc)_2$ in 8 mL of ether was added an ether solution of diazomethane (generated from 3.0 g of 1-methyl-3-nitro-1-nitrosoguanidine) at 0 °C. After stirring at room temperature 20 h solvent was removed and the residue chromatographed to give 4-nitro-7-cyclopropyl-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole.

Example 8.

Halogenation of the 4-amino-7-(4-hydroxybutyl)-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole.

To a cold (0 °C) solution of 1.0 mmol of 4-amino-7-(4-hydroxybutyl)-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole in 20 mL of CH_2Cl_2 was added 3.0 mmol of PPh_3 and 3.0 mmol of CBr_4. After 40 min. at room temperature solvent was removed and the residue was subjected to chromatography to give 4-amino-7-(4-bromobutyl)-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole. CCl_4 gave the corrosponding chloro compound.

Example 9:

General procedures for reduction:

Method A:

A mixture of 1.0 mmol of alkylation product and 20 mg of 10 % Pd/C in 5 mL of DMF or MeOH was hydrogenated using H_2 from a balloon for 0.5-16 h. The reaction mixture was filtered through Celite and chromatographed to provide the reduction product as an oil.

Method B:

To a solution of 1.0 mmol of substituted nitroaniline in 15 mL of MeOH was added 15 mL of a saturated solution of sodium dithionite. Filtration followed by removal of solvent and extraction with EtOAc or $CHCl_3$ provided the pure diamine.

These primary aromatic amines can also be modified as needed. For example N-acetyl derivetives can be prepared by treatment with acetyl chloride or acetic anhydride in presence of a base such as pyridine and mono-, or di-

alkylamines can be synthesized by direct alkylation (see Example 5) or by reductive alkylation (see Example 3, Method C.).

Example 10.

Bromination of 4-amino-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole.

A mixture of 1.0 mmol of 4-amino-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole, and 1.0 mmol of NBS in 5 mL of CCl_4 was stirred at room temperature for 4 h. The mixture was processed by filtration and chromatography to provide o-bromo (21%, R_f= 0.14), p-bromo (25%, R_f= 0.01) and dibromo (36%, R_f= 0.23).

When Br_2 was used in place of NBS, the dibromo compound was formed exclusively. The same procedures were followed for chlorination.

General procedures for phosphonate hydrolysis:

Example 11:

BBr_3 hydrolysis:

To a solution of 1.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole in 3 mL of anhydrous CH_2Cl_2 was added 10 mmol of 1.0 M BBr_3 solution in CH_2Cl_2 at -78°C and the mixture was allowed to warm to room temperature. After 16 h, solvent and excess BBr_3 were removed under reduced pressure and the residue was taken into 3 mL of water. The precipitate was filtered, washed with water, and MeOH and was dried under vaccum at 50° C.

The following compound was prepared in this manner:

11.1: 4-Amino-5-hydroxy-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 206-209 °C; Anal. Cald. for $C_{15}H_{18}N_3O_5P$ + $2.7H_2O$: C: 45.05; H: 5.90; N: 10.51. Found: C: 44.96; H: 5.78; N: 10.14.

Example 12:

TMSBr hydrolysis:

To a solution of 1.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole in 5 mL of anhydrous CH_2Cl_2 was added 10.0 mmol TMSBr at 0 °C. After 16 h stirring at room temperature the solvent and excess TMSBr were removed under reduced pressure. The residue was taken into 15 mL of a 1/5 mixture of acetone/water and was stirred

for 16 h at room temperature. The resulting solid was filtered, washed with water, EtOAc, and MeOH and was dried under vacuum at 50°C.

The following compounds were prepared in this manner:

12.1: 4-Amino-1-ethyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >250 °C; Anal. Cald. for $C_{13}H_{14}N_3O_4P$ + 1 H_2O: C: 48.01; H: 4.96; N: 12.92. Found: C: 48.46; H: 4.79; N: 12.6.

12.2: 4-Amino-1-cyclohexylethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >250 °C; Anal. Cald. for $C_{19}H_{24}N_3O_4P$ + 0.5 H_2O: C: 57.28; H: 6.32; N: 10.55. Found: C: 57.04; H: 5.77; N: 10.32.

12.3: 4-Amino-2-[2-(5-phosphono)furanyl]benzimidazole. mp >240 °C ; Anal. Cald. for $C_{11}H_{10}N_3O_4P$ + $2H_2O$: C: 41.91; H: 4.48; N: 13.33. Found: C: 41.52; H: 4.34; N: 13.09.

12.4: 4-Amino-1-methyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >230 °C ; Anal. Cald. for $C_{12}H_{12}N_3O_4P$ + 1 H_2O: C: 46.31; H: 4.53; N: 13.50. Found: C: 46.52; H: 4.31; N: 13.37.

12.5: 4-Amino-1-(4-methylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole acetic acid salt. mp = 222-225 °C ; Anal. Cald. for $C_{19}H_{18}N_3O_4P$ + AcOH $0.25H_2O$: C: 56.31; H: 5.06; N: 9.38. Found: C: 56.50; H: 5.23; N: 9.63.

12.6: 4-Amino-1-(3-carbomethoxybenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 198-202 °C ; Anal. Cald. for $C_{20}H_{18}N_3O_6P$: C: 55.55; H: 4.39; N: 9.63. Found: C: 55.12; H: 4.29; N: 9.18.

12.7: 4-Amino-1-isobutyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp = 195-200 °C ; Anal. Cald. for $C_{15}H_{18}N_3O_4P$ +1.5 H_2O: C: 49.73 ; H: 5.84; N: 11.60. Found: C: 50.08; H: 5.51; N: 11.23.

12.8: 4-Amino-1-ethylbenzimidazol-2-yl-methyleneoxymethyl phosphonic acid. mp = 208-210 °C ; Anal. Cald. for $C_{11}H_{16}N_3O_4P$ + $2.5H_2O$: C: 40.00; H: 6.41; N: 12.72. Found: C: 40.14; H: 5.17; N: 12.37. >88% pure by HPLC.

12.9: 4-Amino-1-(3-methylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp>250 °C ; Anal. Cald. for $C_{19}H_{18}N_3O_4P$ + H_2O: C: 56.86; H: 5.02; N: 10.47. Found: C: 56.66; H: 4.59; N: 10.34.

12.10: 4-Amino-1-[2'-(3"-carboethoxy-5",6",7",8"-tetrahydronaphthyl)ethyl]-2-[2-(5-phosphono)furanyl]benzimidazole. mp 198-202 °C ; Anal. Cald. for $C_{26}H_{28}N_3O_6P$ + H_2O: C: 59.20; H: 5.73; N: 7.97. Found: C: 59.23; H: 5.54; N: 7.68.

12.11: 4-Amino-1-[2'-(3"-carboxy-5",6",7",8"-tetrahydronaphthyl)ethyl]-2-[2-(5-phosphono)furanyl]benzimidazole. mp = 220-224 °C ; Anal. Cald. for

$C_{24}H_{24}N_3O_6P + 2H_2O$: C: 55.71; H: 5.45; N: 8.12. Found: C: 56.18; H: 5.17; N: 7.97.

12.12: 4-Amino-1-propyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >230 °C ; Anal. Cald. for $C_{14}H_{16}N_3O_4P + 1.25\ H_2O$: C: 48.91; H: 5.42; N: 12.22. Found: C: 48.88; H: 5.07; N: 12.26.

12.13: 4-Amino-1-norbornylmethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{19}H_{22}N_3O_4P + 0.75H_2O$: C: 56.93; H: 5.91; N: 10.48. Found: C: 56.97; H: 5.63; N:10.28.

12.14: 4-Amino-1-(3-carboxybenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >250 °C ; Anal. Cald. for $C_{19}H_{16}N_3O_6P + 2.5H_2O$: C: 49.79; H: 4.62; N: 9.17. Found: C: 49.30; H: 4.00; N: 8.49. Mass. cald. for $C_{19}H_{16}N_3O_6P$: 413. Found: $MH^+ = 414$: $MH^- = 412$.

12.15: 4-Amino-1-cyclopentanemethyl-2-[2-(5-phosphono)furanyl]-benzimidazole. mp >230 °C; Anal. Cald. for $C_{17}H_{20}N_3O_4P + 1.4H_2O$: C: 52.82; H: 5.92; N: 10.87. Found: C: 52.81; H: 5.71; N: 10.51.

12.16: 4-Amino-1-cyclopropanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{15}H_{16}N_3O_4P + 0.75\ CH_2Cl_2$: C: 47.65; H: 4.44; N: 10.58. Found: C: 47.81; H: 4.57; N: 10.77.

12.17: 4-Amino-1-cyclobutanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{16}H_{18}N_3O_4P + 0.5\ H_2O$: C: 53.93; H: 5.37; N: 11.79. Found: C: 53.89; H: 5.12; N: 11.48.

12.18: 4-Amino-1-(3-methyl-6,6-dimethyl-2-cyclohexenylmethyl)-2-[2-(5-phosphono)furanyl]benzimidazole. mp >220 °C ; Anal. Cald. for $C_{21}H_{24}N_3O_4PNa_2 + 2\ H_2O$: C: 50.91; H: 5.70; N: 8.48. Found: C: 50.82; H: 5.53; N: 8.26.

12.19: 4-Amino-1-(2-methyl-2-butenyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 190-195 °C ; Anal. Cald. for $C_{16}H_{18}N_3O_4P + 1.5H_2O$: C: 51.34; H: 5.65; N: 11.23. Found: C: 51.68; H: 5.59; N: 11.37.

12.20: 4-Amino-1-[(1S,2S,5S)myrtanyl]-2-[2-(5-phosphono)furanyl] benzimidazole. mp>200 °C ; Anal. Cald. for $C_{21}H_{26}N_3O_4P + 1H_2O$: C: 58.19; H: 6.51; N: 9.69. Found: C: 58.49; H: 6.12; N: 9.65.

12.21: 4-Amino-1-(4-t-butylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 246-249 °C ; Anal. Cald. for $C_{22}H_{21}N_3O_4P + 0.66H_2O$: C: 60.40; H: 5.84; N: 9.60. Found: C: 60.37; H: 5.45; N: 8.87.Mass. cald. for $C_{22}H_{21}N_3O_4P = 425$. Found: $MH^+ = 426$; $MH^- = 424$.

12.22: 4-Amino-1-(4-cyclohexyl-1-butyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >230 °C ; Anal. Cald. for $C_{21}H_{28}N_3O_4P$ + $0.6H_2O$: C: 58.90; H: 6.87; N: 9.81. Found: C: 58.67; H: 6.54; N: 9.46.

12.23: 4-Amino-1-(3-cyclohexyl-1-propyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >218 °C ; Anal. Cald. for $C_{20}H_{26}N_3O_4P$ + 1.2 H_2O: C: 56.52; H: 6.73; N: 9.89. Found: C: 56.71; H: 6.30; N: 9.47.

12.24: 4-Amino-1-(3-carboxypropyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >225 °C ; Anal. Cald. for $C_{15}H_{16}N_3O_6P$: C: 49.3; H: 4.42; N: 11.51. Found: C: 49.01; H: 4.22; N: 11.21.

12.25: 4-Amino-1-(3-carboethoxypropyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >225 °C; Anal. Cald. for $C_{17}H_{20}N_3O_6P$: C: 51.89; H: 5.13; N: 10.69. Found: C: 51.68; H: 5.08; N: 10.34.

12.26: 4-Amino-1-(t-butylmethylketone)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >225 °C ; Anal. Cald. for $C_{17}H_{20}N_3O_5P$ + 1.3 H_2O: C: 50.95; H: 5.68; N: 10.49. Found: C: 50.83; H: 5.21; N: 9.85.

12.27: 4-Amino-1-cycloheptanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp 198 °C ; Anal. Cald. for $C_{19}H_{24}N_3O_4P$ + 0.5 H_2O: C: 57.27; H: 6.25; N: 10.02. Found: C: 57.46; H: 6.22; N: 9.86.

12.28: 4-Amino-1-cyclohexanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp 210 °C ; Anal. Cald. for $C_{18}H_{22}N_3O_4P$ + 0.5 AcOH: C: 56.29; H: 5.97; N: 10.37. Found: C: 56.00; H: 5.96; N: 10.32.

12.29: 4-Amino-1-benzyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >250 °C ; Anal. Cald. for $C_{18}H_{14}N_3O_4PNa_2$ + $1.6H_2O$: C: 48.78; H: 3.94; N: 9.48. Found: C: 49.10; H: 4.11; N: 8.73. Mass. cald. for $C_{18}H_{16}N_3O_4P$ = 369. Found: MH^+ = 370; MH^- = 368.

12.30: 4-Amino-1-(3-trifluoromethylbenzyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp 235-239 °C ; Anal. Cald. for $C_{19}H_{15}N_3O_4PF_3$ +0.1 H_2O +$1.6CH_3CO_2H$: C: 49.82; H: 4.07; N: 7.85. Found: C: 50.31; H: 4.04; N: 7.38.

12.31: 4-Amino-1-(3-carbamoylpropyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >225 °C ; Anal. Cald. for $C_{15}H_{17}N_4O_5P$: C: 49.44; H: 4.71; N: 15.38. Found: C: 49.00; H: 5.47; N: 14.06. Mass. cald. for $C_{15}H_{17}N_4O_5P$ = 364; MH^+ = 365: MH^- = 363.

12.32: 4-Amino-1-(7-hydroxy-3R,7-dimethyloctyl)-2-[2-(5-phosphono)furanyl]benzimidazole. mp >250 °C ; Anal. Cald. for $C_{21}H_{28}N_3O_5PNa_2$ + 1.5 H_2O: C: 49.80; H: 6.17; N: 8.30. Found: C: 49.43; H: 6.01; N: 8.10.

12.33: 4-Amino-1-(4-chlorobutyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >240 °C ; Anal. Cald. for $C_{15}H_{17}N_3O_4ClP$ + 0.5 H_2O: C: 47.57; H: 4.79; N: 11.09. Found: C: 47.62; H: 4.57; N: 10.87.

12.34: 4-Amino-1-(4-phenylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >220 °C ; Anal. Cald. for $C_{24}H_{20}N_3O_4P$ + 0.66 H_2O: C: 63.01; H: 4.70; N: 9.19. Found: C: 63.09; H: 4.50; N: 8.81.

12.35: 4-Amino-1-(3-chloropropyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>250 °C ; Anal. Cald. for $C_{14}H_{15}N_3O_4ClP$ + 0.7 H_2O: C: 44.83; H: 4.61; N: 10.37. Found: C:44.50; H:4.29; N:10.96.

12.36: 4-Amino-1-(4-hydroxybutyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>250 °C ; Anal. Cald. for $C_{15}H_{16}N_3O_5PNa_2$ + 1.8 H_2O: C: 41.68; H: 4.71; N: 9.04. Found: C: 41.29; H: 4.60; N: 9.31.

12.37: 4-Amino-1-(3-furanylmethyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>230 °C ; Mass. Cald. 358; Obs. 358.

12.38: 4-Amino-1-(3-hydroxybenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp 232-4 °C ; Anal. Cald. for $C_{18}H_{16}N_3O_5P$ + 2 H_2O: C: 51.31; H: 4.78; N: 9.97. Found: C: 51.01; H: 4.72; N: 10.15.

12.39: 4-Amino-1-[(2-methoxy)phenethyl]-2-[2-(5-phosphono)furanyl] benzimidazole. mp >240 °C ; Anal. Cald. for $C_{20}H_{20}N_3O_5P$ + 1 H_2O: C: 55.69; H: 5.14; N: 9.64. Found: C: 55.2; H: 4.90; N: 9.35.

12.40: 4-Amino-1-[(3-methoxy)phenethyl]-2-[2-(5-phosphono)furanyl] benzimidazole. mp >240 °C ; Anal. Cald. for $C_{20}H_{20}N_3O_5P$ + 1 H_2O: C: 55.69; H: 5.14; N: 9.64. Found: C: 55.09; H: 4.71; N: 9.52.

12.41: 4-Amino-1-(3-thienylmethyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 200-205 °C ; Anal. Cald. for $C_{16}H_{14}N_3O_4PS$ + 1.7 H_2O: C: 47.34; H: 4.32; N: 10.35. Found: C: 46.90; H: 3.88; N: 10.05.

12.42: 4-Amino-5,7-dibromo-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >215 °C ; Anal. Cald. for $C_{15}H_{16}Br_2N_3O_4P$: C:36.54; H: 3.27; N: 8.52. Found: C: 36.55; H: 3.22; N: 8.13.

12.43: 4-Amino-1-(1-hydroxyprop-3-yl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >213 °C ;.Mass. Cald. 336; Obs. 336.

12.44: 4-Amino-5-bromo-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >239 °C ; Anal. Cald. for $C_{15}H_{17}N_3O_4BrP$ + 0.5 H_2O: C: 42.57; H: 4.29; N: 9.93. Found: C: 42.44; H: 3.99; N: 9.69.

12.45: 4-Amino-1-ethyl-2-[1-(2-phosphonomethyloxy)phenyl] benzimidazole. mp 180-185 °C ; Anal. Cald. for $C_{16}H_{18}N_3O_4P$ + 0.8 H_2O: C: 53.13; H: 5.46; N: 11.62. Found: C: 52.98; H: 5.20; N: 11.32.

12.46: 4-Amino-7-bromo-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{15}H_{17}N_3O_4BrP$ + 0.25 H_2O: C: 43.03; H: 4.21; N: 10.04. Found: C: 42.69; H:3.87; N: 9.63.

12.47: 4-Amino-7-bromo-1-cyclobutanemethyl-2-[2-(5-phosphono) furanyl]benzimidazole. mp >200 °C ; Anal. Cald. for $C_{16}H_{17}BrN_3O_4P$ + H_2O + 0.06 EtOAc: C: 43.24; H: 4.33; N: 9.38. Found: C: 43.40; H: 3.95; N: 9.11.

12.48: 4-Amino-5-bromo-1-cyclobutanemethyl-2-[2-(5-phosphono) furanyl]benzimidazole. mp >200 °C ; >91% pure by HPLC.

12.49: 4-Amino-5-chloro-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>240 °C ; Anal. Cald. for $C_{15}H_{17}ClN_3O_4P$ + 0.8H_2O: C: 46.90; H: 4.88; N: 10.94. Found: C: 46.99; H: 4.53; N: 10.76.

12.50: 4-Amino-5,7-dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 205-207 °C; Anal.Cald. for $C_{15}H_{16}N_3O_4Cl_2P$ + 0.5H_2O: C: 43.60; H: 4.15; N: 10.17. Found: C: 43.64; H: 4.03; N: 10.02.

12.51: 4-Amino-1-(2-thienylethyl)-2-[2-(5-phosphono)furanyl benzimidazole. mp = 225 °C; Anal. Cald. for $C_{17}H_{16}N_3O_4PS$+1.1H_2O. C: 50.12; H: 4.45 N: 10.31. Found: C: 49.67; H: 3.96; N: 10.45.

12.52: 4-Amino-5-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 220-225 °C; Anal. Cald. for C: 51.34; H: 5.95; N: 10.21.

12.53: 4-Amino-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 230-235 °C; Anal. Cald. for $C_{15}H_{17}N_3O_4PF$ + 0.8 H_2O; C: 49.00; H: 5.10; N: 11.43. Found: C: 49.13; H: 4.81; N: 11.13.

12.54: 4-Amino-5-fluoro-7-chloro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 220-225 °C; Anal. Cald. for $C_{15}H_{16}N_3O_4FClP$ + 0.9 HBr; C: 12; H: 3.70; N: 9.12. Found: C: 39.15; H: 3.46; N: 8.77.

12.55: 4-Amino-5-methoxy-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 212-213 °C; Anal. Cald. for $C_{16}H_{20}N_3O_5P$+H_2O: C: 50.13; H: 5.78; N: 10.96. Found: C: 49.93; H: 5.55; N: 10.79.

12.56: 4-Amino-2-[2-(5-phosphono)furanyl]-1-[(3-amino)phenethyl] benzimidazole. mp = 297 °C; Anal. Cald. for $C_{19}H_{19}N_4O_4P$ + 0.4 AcOH + 0.1 MeCN + 1.5 H_2O: C: 52.97; H: 5.31; N: 12.66. Found: C: 52.83; H: 5.17; N: 11.99. Found: C: 52.65; H: 4.92; N: 12.14.

12.57: 4-Amino-1-[(2-ethyl)pentyl]benzimidazol-2-yl-methylenoxymethyl phosphonic acid. mp = 85 °C; Anal. Cald. for $C_{15}H_{24}N_3O_4P$ + 1/2 H_2O + 2 HBr + 1/3 toluene: C: 38.05; H: 5.49; N: 7.78. Found: C: 38.30; H: 5.45; N: 7.34.

12.58: 4-Amino-5-bromo-6,7-dichloro-2-(2-phosphono-5-furanyl) benzimidazole. mp = 224-225 °C; Anal. Cald. for : C: 38.92; H: 3.23; N: 5.92

12.59: 5-Amino-2-(2-Phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_{10}N_3PO_4$ + CF_3CO_2H + 1.5 H_2O: C: 37.16; H: 3.36; N: 10.00. Found: C: 37.40; H: 3.31; N: 9.77.

12.60: 4-Amino-5-propyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 207-210 °C; Anal. Cald. for $C_{18}H_{24}N_3PO_4$ + 2 H_2O: C: 52.30; H: 6.83; N: 10.16. Found: C: 52.05; H: 6.71; N: 9.95.

12.61: 4-Amino-5-fluoro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 258- 260 °C; Anal. Cald. for $C_{15}H_{15}N_3O_4P$ F + 0.3 H_2O: C: 50.51; H: 4.41; N: 11.78. Found: C: 50.21; H: 4.28; N: 11.45.

12.62: 4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 195-200 °C; Anal. Cald. for $C_{15}H_{16}N_3BrFPO_4$: C: 41.69; H: 3.73; N: 9.72. Found: C: 41.59; H: 3.81; N: 9.67.

12.63: 4-Amino-5-fluoro-6-chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 175-180 °C; Anal. Cald. for $C_{15}H_{16}N_3ClFPO_4$ + 2.0 H_2O: C: 42.52; H: 4.76; N: 9.92. Found: C: 42.60; H: 4.56; N: 9.81.

12.64: 4-Amino-7-ethyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 245-246 °C; Anal. Cald. for $C_{17}H_{21}N_3O_4FP$ + 0.4 H_2O: C: 52.55; H: 5.66; N: 10.81. Found: C: 52.40; H: 5.79; N: 10.47.

12.65: 7-Amino-4-ethyl-6-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 249-250 °C; Anal. Cald. for $C_{17}H_{21}N_3O_4FP$: C: 53.54; H: 5.55; N: 11.02. Found: C: 53.20; H: 5.38; N: 10.73.

12.66: 4-Amino-7-cyclopropyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 250-255 °C (dec.); Anal. Cald. for $C_{18}H_{21}N_3O_4FP$ + 0.25 H_2O: C: 54.34; H: 5.45; N: 10.56. Found: C: 54.14; H: 5.28; N: 10.31.

12.67: 4-Amino-7-phenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 240-241 °C (dec.); Anal. Cald. for $C_{21}H_{21}N_3O_4FP$ + 0.05H_2O: C: 58.62; H: 4.94; N: 9.77. Found: C: 58.27; H: 4.86; N: 9.47.

12.68: 4-Amino-7-p-fluorophenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 239-240 °C (dec.); Anal. Cald. for $C_{21}H_{20}N_3O_4F_2P$: C: 56.38; H: 4.51; N: 9.39. Found: C: 56.38; H: 4.36; N: 9.14.

12.69: 4-Amino-7-p-chlorophenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 235-236 °C (dec.); Anal. Cald. for $C_{21}H_{20}N_3O_4FClP$: C: 54.38; H: 4.35; N: 9.06. Found: C: 54.10; H: 4.20; N: 8.73.

12.70: 4-Amino-7-vinyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 238-242 °C; Anal. Cald. for $C_{17}H_{19}N_3O_4FP$ + 1.2 H_2O: C: 50.93; H: 5.38; N: 10.48. Found: C: 51.07; H: 5.37; N: 10.12.

12.71: 4-Amino-7-(4-methylpentane)-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 185-195 °C (dec.); Anal. Cald. for $C_{21}H_{29}N_3O_4FP$+0.25 H_2O: C: 57.07; H: 6.73; N: 9.51. Found: C: 57.03; H: 6.89; N: 9.24.

12.72: 4-Amino-7-(3,3-dimethylbutane)-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 200-205 °C (dec.); Anal. Cald. for $C_{21}H_{29}N_3O_4FP$ + 0.75 H_2O: C: 55.93; H: 6.82; N: 9.32. Found: C: 55.84; H: 6.62; N: 9.15.

12.73: 4-Amino-5-fluoro-1-(2-ethylbutyl)-2-(2-phosphono-5-furanyl)benzimidazole. mp = 178-182 °C (dec.); Anal. Cald. for $C_{17}H_{21}N_3O_4FP$ + 1.0 H_2O: C: 51.13; H: 5.80; N: 10.52. Found: C: 51.03; H: 5.58; N: 10.27.

12.74: 4-Amino-7-m-methoxyphenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 208-212 °C (dec.); Anal. Cald. for $C_{22}H_{23}N_3O_5FP$ + 0.25 H_2O: C: 56.96; H: 5.11; N: 9.06. Found: C: 57.02; H: 5.14; N: 8.52.

12.75: 4-Amino-7-ethyl-5-fluoro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 178-185 °C; Anal. Cald. for $C_{17}H_{19}N_3O_4FP$ + 1.3 H_2O: C: 50.70; H: 5.41; N: 10.43. Found: C: 50.98; H: 5.29; N: 10.05.

12.76: 4-Amino-5-fluoro-1-(3-pentyl)-2-(2-phosphono-5-furanyl)benzimidazole. mp = 180-185 °C (dec.); Anal. Cald. for $C_{16}H_{19}N_3O_4FP$ + 1.5 H_2O: C: 48.73; H: 5.62; N: 10.66. Found: C: 48.60; H: 5.55; N: 10.49.

12.77:5,6,7-Trifluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 250-260 °C; Anal. Cald. for $C_{15}H_{14}N_2O_4F_3P$: C: 48.14; H: 3.77; N: 7.49. Found: C: 48.04; H: 3.81; N: 7.43.

12.78:4,5,6-Trifluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 155-158 °C; Anal. Cald. for $C_{15}H_{14}N_2O_4F_3P$: C: 48.14; H: 3.77; N: 7.49. Found: C: 48.04; H: 3.81; N: 7.43.

12.79: 4-Amino-7-(propane-3-ol)-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 170-173 °C; Anal. Cald. for $C_{18}H_{23}N_3O_5FP$ + 1.0 H_2O: C: 50.35; H: 5.87; N: 9.79. Found: C: 50.31; H: 5.80; N: 9.62.

12.80: 4-Amino-5-fluoro-7-(3-bromopropyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 190-195 °C (dec.); Anal. Cald. for $C_{18}H_{22}N_3O_4FBrP$: C: 45.59; H: 4.68; N: 8.86. Found: C: 45.87; H: 4.87; N: 8.70.

12.81: 4-Amino-5-fluoro-7-n-propyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 220-230 °C (dec.); Anal. Cald. for $C_{18}H_{23}N_3O_4FP$ + 0.85 H_2O: C: 52.64; H: 6.06; N: 10.23. Found: C: 53.00; H: 6.09; N: 9.70.

12.82: 4-Amino-5-fluoro-7-(4-bromobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 200-220 °C (dec.); Anal. Cald. for $C_{19}H_{24}N_3O_4FBrP$ + 0.5 H_2O: C: 45.89; H: 5.07; N: 8.45. Found: C: 45.61; H: 5.10; N: 8.20.

12.83: 4-Amino-5-fluoro-7-(4-chlorobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 210-220 °C (dec.); Anal. Cald. for $C_{19}H_{24}N_3O_4FClP$ + 0.25 H_2O: C: 50.90; H: 5.51; N: 9.37. Found: C: 50.96; H: 5.53; N: 9.13.

12.84: 4-Amino-5-fluoro-7-(3-N,N-dimethylpropylamine)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole hydrobromide salt. mp = 208-212 °C (dec.); Anal. Cald. for $C_{20}H_{28}N_4O_4FP$ + 1.0 Hbr + 2.0 H_2O: C: 43.25; H: 5.99; N: 10.09. Found: C: 43.39; H: 5.74; N: 9.90.

12.85: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(2-phosphono-5-thionyl)benzimidazole. Anal. Cald. for $C_{17}H_{18}N_2O_3PSCl$: C: 51.45; H: 4.57; N: 7.06; Found: C: 51.28; H: 4.58; N: 6.92.

12.86: 4-Amino-5-fluoro-7-ethyl-1-2(2-phosphono-5-furanyl)benzimidazole. mp = 180-186° C; Anal. Cald. for $C_{13}H_{13}N_3O_4FP$ + 1.2 H_2O: C: 45.02; H: 4.48, N: 12.11. Found: C: 45.17; H: 4.52; N: 11.81.

Example 13:

HBr hydrolysis:

A solution of 1.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole in 10 ml of 30 % HBr was heated at 80° C for 0.5-3 h. The solvent was removed under reduced pressure and the

residue was taken into 3 ml of water. The solid precipitated was filtered washed with water and dried under vaccum at 50°C.

The following compounds were prepared in this manner:

13.1: 2-(2-Phosphono-5-furanyl)benzimidazole. mp>250 °C ; Anal. Cald. for $C_{11}H_9N_2O_4P$ + 0.55 HBr + H_2O: C: 40.44; H: 3.56; N: 8.57. Found: C: 40.74; H: 3.51; N: 8.53.

13.2: 1-Isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 200-203 °C; Anal. Cald. for $C_{15}H_{17}N_2O_4P$ + 0.75 H_2O: C: 53.97; H: 5.59; N: 8.39. Found: C: 53.70; H: 5.37; N: 8.24.

13.3: 2-[5,6-Indano-1(H)-imidazol-2-yl]furan-5-phosphonic acid. Anal. Cald. for $C_{14}H_{13}N_2PO_4$ + 1.25 H_2O: C: 51.46; H: 4.78; N:.8.57. Found: C: 51.43; H: 4.38; N: 8.44.

13.4: 2-(1-Isobutyl-5,6-indanoimidazol-2-yl)furan-5-phosphonic acid. Anal. Cald. for $C_{18}H_{21}N_2PO_4$ + 0.5 H_2O: C: 58.53; H: 6.00; N: 7.58. Found: C: 58.45; H: 5.62; N: 7.44.

13.5: 2-(1,8-Diaza-1,2,3,4-tetrahydroacenaphthen-9-yl)furan-5-phosphonic acid. Anal. Cald. for $C_{14}H_{13}N_2PO_4$ + 0.5 HBr + 0.5 H_2O: C: 47.54; H: 4.13; N: 7.48. Found: C: 47.33; H: 4.16; N: 7.48.

13.6: 2-(2-Phosphono-5-furanyl)-5-trifluoromethylbenzimidazole. Anal. Cald. for $C_{12}H_8F_3N_2O_4P$ + 1.2 H_2O. C: 40.74; H: 2.96; N: 7.92; F: 16.11. Found: C: 40.49; H: 2.71; N: 7.89; F: 16.50.

13.7: 2-(2-Phosphono-5-furanyl)-5-fluorobenzimidazole. Anal. Cald. for $C_{11}H_8FN_2O_4P$ + 2/3 H_2O. C: 44.93; H: 3.19; N: 9.53; F: 6.46. Found: C: 44.91 H: 3.05; N: 9.34; F: 6.54.

13.8: 2-(2-Phosphono-5-furanyl)-5,6-dichlorobenzimidazole. Anal. Cald. for $C_{11}H_7Cl_2N_2O_4P$ + 0.25 AcOH; C: 39.68; H: 2.32; N: 8.05; Cl: 20.37. Found: C: 39.92; H: 2.28; N: 7.87; Cl: 20.10.

13.9: 2-(2-Phosphono-5-furanyl)-5-chlorobenzimidazole. Anal. Cald. for $C_{11}H_8ClN_2O_4P$ + 0.75 HBr + 0.33 H_2O; C: 36.17; H: 2.60; N: 7.67; Cl: 9.71. Found: C: 36.53; H: 2.43; N: 7.31; Cl: 9.48.

13.10: 2-(2-Phosphono-5-furanyl)-5-methylbenzimidazole. Anal. Cald. for $C_{12}H_{11}N_2PO_4$ + H_2O: C: 48.66; H: 4.42; N: 9.46. Found: C: 48.64; H: 4.20; N: 9.22.

13.11: 2-(2-Phosphono-5-furanyl)-5-(tert-butyl)benzimidazole. Anal. Cald. for $C_{15}H_{17}N_2PO_4$ + H_2O: C: 53.26; H: 5.66; N: 8.28. Found: C: 53.04; H: 5.57; N: 7.96.

13.12: 1-Phenyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 196- 200 °C; Anal. Cald. for $C_{17}H_{13}N_2PO_4$ + 2 H_20 + HBr: C: 44.66; H: 3.97; N: 6.13 . Found: C: 45.06; H: 3.66; N: 6.01.

13.13: 1-(2-Carboxyphenyl)-2-(2-phosphono-5-furanyl)-5-chloro benzimidazole. mp = 220- 224 °C; Anal. Cald. for $C_{18}H_{12}N_2O_6ClP$ + H_2O + 0.2 HBr: C: 47.73; H: 3.16; N: 6.18; Cl: 7.83. Found: C: 48.07; H: 2.86 N: 5.98; Cl: 7.78.

13.14: 5-Nitro-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_8N_3PO_6$ + H_2O: C: 40.38; H: 3.08; N: 12.84. Found: C: 40.28; H: 2.97; N: 12.47.

13.15: 4,5-Dimethyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{13}H_{13}N_2PO_4$ + 0.6 H_2O: C: 51.53; H: 4.72; N: 9.24. Found: C: 51.20; H: 4.64; N: 9.13.

13.16: 5-Chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 238 °C; Anal. Cald. for $C_{15}H_{16}ClN_2O_4P$ + 0.33 HBr; C: 47.23; H: 4.32; N: 7.34; Cl: 9.29. Found: C: 47.37; H: 4.02; N: 6.99; Cl: 9.56.

13.17: 6-Chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{16}ClN_2O_4P$ + 0.5 HBr: C: 45.59; H: 4.21; N: 7.09; Cl: 8.97. Found: C: 46.02; H: 3.86; N: 7.01; Cl: 8.63.

13.18: 5-Benzophenone-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{18}H_{13}N_2O_5P$ + 1.75 H_2O + .25 HBr: C: 51.47; H: 4.02; N: 6.67. Found: C: 51.63; H: 4.09; N: 6.31.

13.19: 4-Amidinomethyl-2-[2-(5-phosphono)furanyl]-1-[(2-ethyl) pentyl]benzimidazole. mp = 225-230 °C; Anal. Cald. for $C_{19}H_{25}N_4O_4P$ + 0.3 H_2O: C: 55.69; H: 6.30; N: 13.67. Found: C: 55.46; H: 5.77; N: 13.16.

13.20: 1-Isobutyl-4-isobutyloxy-2-(2-phosphono-5-furanyl) benzimidazole. mp = 350 °C; Anal. Cald. for $C_{19}H_{25}N_2O_5P$ + 1.0 H_2O: C: 55.61; H: 6.63; N: 6.83. Found: C: 55.26; H: 6.41; N: 6.59.

13.21: 4-Hydroxy-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 244-245 °C; Anal. Cald. for $C_{15}H_{17}N_2O_5P$ + 1.1 H_2O: C: 50.59; H: 5.43; N: 7.87. Found: C: 50.33; H: 5.38; N: 7.89.

13.22: 5,6-Difluoro-2-(2-Phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7N_2PO_4F_2$ + 0.3 H_20: C: 43.24; H: 2.51; N: 9.17; F: 12.44. Found: C: 43.58; H: 2.63; N: 8.69; F: 12.28.

13.23: 2-(2-Phosphono-5-furanyl)benzimidazole-5-methylcarboxylate. Anal. Cald. for $C_{13}H_{11}N_2O_6P$ + 0.5 H_2O + 0.25 HBr: C: 44.43; H: 3.51; N: 7.97; Found: C: 44.41; H: 3.80; N: 8.16.

13.24: 5,6-Dimethyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{13}H_{13}N_2O_4P$ + 2/3 H_2O: C: 51.34; H: 4.75; N: 9.21. Found: C: 51.48: H: 4.75; N: 8.95.

13.25: 4-Fluoro-1-neopentyl-2-(2-phosphonofuranyl)benzimidazole. Anal. Cald. for $C_{16}H_{18}N_2PO_4F$ + 0.1 H_2O + 0.3 CH_3CO_2H: C: 53.58; H: 5.25; N: 7.53. Found: C: 53.84; H: 5.12; N: 7.05.

13.26: 2-(2-Phosphonofuranyl)-(4,5-benz)benzimidazole. Anal. Cald. for $C_{15}H_{11}N_2PO_4$ + 1.75 H_2O: C: 52.11; H: 4.23; N: 8.10. Found: C: 52.40; H: 4.34; N: 7.70.

13.27: 6-Fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 202-205 °C; Anal. Cald. for $C_{15}H_{16}FN_2O_4P$ +0.25 HBr + 0.5 H_2O: C: 49.02; H: 4.73; N: 7.62. Found: C: 48.90; C: 4.89; N: 7.50.

13.28: 5-Fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{16}FN_2O_4P$ + 0.1 HBr: C: 52.02; H: 4.69; N: 8.09; F: 5.49. Found: C: 52.07; H: 32; N: 7.88; F: 5.61.

13.29: 2-(2-Phosphonofuranyl)-4,5-(2-methylthiazole) benzimidazole. Anal. Cald. for $C_{13}H_{10}N_3O_4PS$ + 2.25 H_2O: C: 41.55; H: 3.89; N: 11.18; S: 8.53. Found: C: 41.69; H: 3.93; N: 10.99; S: 8.81.

13.30: 1-(4-Pyridyl)-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{16}H_{12}N_3PO_4$ + H_20 + 1.25 HBr + 0.5 CH_3CO_2H: C: 41.63; H: 3.55; N: 8.57. Found: C: 41.66; H: 3.52; N: 8.29.

13.31: 2-(2-Phosphonofuranyl)-(4,5-tetramethylene)benzimidazole. Anal. Cald. for $C_{15}H_{15}N_2PO_4$ + 1.5 H_2O: C: 52.18; H: 5.25; N: 8.11. Found: C: 52.09; H: 5.01; N: 7.85.

13.32: 4-Methyl-2-(2-phosphonofuranyl)benzimidazole. Anal. Cald. for $C_{12}H_{11}N_2PO_4$ + H_2O: C: 48.66; H: 4.42; N: 9.46. Found: C: 48.55; H: 4.51; N: 9.16.

13.33: 5-Chloro-1-isopropyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 192 - 195 °C; Anal. Cald. for $C_{14}H_{14}N_2O_4PCl$ + H_2O + 0.1 HBr: C: 45.84; H: 4.42; N: 7.64; Cl=9.67. Found: C: 45.58; H: 4.30; N: 7.47; Cl=10.63.

13.34: 5,6-Difluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{15}F_2N_2O_4P$ + 0.5 H_2O: C: 49.32; H: 4.42; N: 7.67; F: 10.40. Found: C: 49.06; H: 4.20; N: 7.60; F: 10.26.

13.35: 5-Bromo-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_8BrN_2O_4P + H_2O + .05\ HBr$: C: 36.18; H2.77; N: 7.67; Br: 22.98. Found: C: 36.20; H: 2.61; N: 7.45; Br: 22.77.

13.36: 5-Bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{15}H_{16}BrN_2O_4P + .75\ H_2O + .05\ HBr$: C: 43.23; H: 4.24; N: 6.72; Br: 20.13. Found: C: 43.25; H: 4.18; N: 6.59; Br: 20.30.

13.37: 6-Bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{15}H_{16}BrN_2O_4P + H_2O + .05\ HBr$: C: 42.77; H: 4.32; N: 6.65; Br: 19.92. Found: C: 42.49; H: 4.04; N: 6.53; Br: 20.02.

13.38: 4,6-Dichloro-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7N_2O_4PCl_2 + 1.5\ H_2O$: C: 36.69; H: 2.80; N: 7.78; Found: C: 36.91; H: 2.64; N: 7.71.

13.39: 4,6-Dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 155-175 °C; Anal. Cald. for $C_{15}H_{15}N_2O_4PCl_2 + 2/3\ H_2O$: C: 44.90; H: 4.10; N: 6.98. Found: C: 44.96; H: 3.97; N: 6.85.

13.40: 5-Chloro-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{17}H_{12}N_2O_4PCl + 1\ H_2O + 0.1\ HBr$: C: 50.94; H: 3.55; N: 6.99. Found: C: 51.33; H: 3.63; N: 6.54.

13.41: 6-Chloro-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{17}H_{12}N_2O_4PCl + 0.25\ H_2O + 0.1\ HBr$: C: 52.72; H: 3.28; N: 7.23. Found: C: 52.94; H: 2.99; N: 7.03.

13.42: 4,6-Dibromo-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7Br_2N_2O_4P + 1\ H_2O + 0.1\ HBr$: C: 29.49; H: 2.05; N: 6.25. Found: C: 29.56; H: 2.06; N: 6.16.

13.43: 4,6-Dibromo-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 150-210 °C; Anal. Cald. for $C_{15}H_{15}Br_2N_2O_4P + 0.25\ H_2O + 0.1HBr$: C: 36.72; H: 3.20; N: 5.71. Found: C: 36.72; H: 3.24; N: 5.73.

13.44: 5,6-Dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 225-227 °C; Anal. Cald. for $C_{15}H_{15}Cl_2N_2O_4P + 0.25\ H_2O + 0.1\ HBr$: C: 44.84; H: 3.91; N: 6.97. Found: C: 44.86; H: 3.85; N: 6.81.

13.45: 5,6-Dichloro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 180-210 °C; Anal. Cald. for $C_{15}H_{13}Cl_2N_2O_4P + 0.5\ H_2O + 0.1\ HBr$: C: 44.57; H: 3.52; N: 6.93. Found: C: 44.69; H: 3.45; N: 6.66.

13.46: 5-Chloro-6-fluoro-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7ClFN_2O_4P + 0.5\ H_2O$: C: 40.58; H: 2.48; N: 8.60. Found: C: 40.58; H: 2.47; N: 8.29.

13.47: 4-Phenyl-6-trifluoromethyl(2-phosphono-5-furanyl) benzimidazole. $C_{18}H_{12}N_2PO_4F_3 + H_2O$: C: 50.72; H: 3.31; N: 6.57. Found: C: 50.58; H: 3.08; N: 6.35.

13.48: 4-Bromo-6-trifluoromethyl(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{12}H_7N_2PO_4F_3Br + H_2O$: C: 33.59; H: 2.11; N: 6.53. Found: C: 33.53; H: 1.86; N: 6.43.

13.49: 5-Chloro-6-fluoro-1-methylcyclopropyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{13}N_2PO_4ClF$: C: 48.60; H: 3.53; N: 7.56. Found: C: 48.32; H: 3.55; N: 7.31.

13.50: 5-Chloro-6-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 196-199; Anal. Cald. for $C_{15}H_{15}ClFN_2O_4P + 1.75\ H_2O$: C: 44.57; H: 4.61; N: 6.93. Found: C: 44.45; H: 4.58; N: 6.87.

13.51: 4-Amino-5-hydroxy-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 206-209 °C; Anal. Cald. for $C_{15}H_{18}N_3O_5P + 2.7\ H_2O$: C: 45.05; H: 5.90; N: 10.51. Found: C: 44.96; H: 5.78; N: 10.14.

13.52: 5-Phosphonomethylenoxy-1,2,3,4-tetrahydropyrido[1,2-a] benzimidazole. mp = 218-222 °C; Anal. Cald. for $C_{12}H_{15}N_2PO_4 + H_2O + 0.9\ HBr$: C: 38.63; H: 4.84; N: 7.51. Found: C: 38.96; H: 4.46; N: 7.41.

13.53: 4,5-Dimethyl-6-bromo-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 205-209 °C; Anal. Cald. for $C_{17}H_{20}PN_2O_4Br + 0.25\ H_2O$: C: 47.29; H: 4.79; N: 6.49. Found: C: 47.25; H: 4.77; N: 6.06.

13.54: 4-Methyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 208-211 °C; Anal. Cald. for $C_{16}H_{19}N_2O_4P + H_2O + 0.25\ HBr$: C: 51.58; H: 5.75; N: 7.52. Found: C: 51.49; H: 5.88; N: 7.41.

13.55: 7-Methyl-1-neopentyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$: C: 58.62; H: 6.08; N: 8.04; Found: C: 58.35; H: 5.97; N: 7.92.

13.56: 6-Chloro-1-neopentyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{16}H_{18}N_2O_4PCl{+}0.5\ H_2O$: C: 50.87 H: 5.07 N: 7.42; C: 50.88 H: 4.82 N: 7.29.

13.57: 5-Chloro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{14}N_2O_4PCl + 0.75\ H_2O$: C: 49.39; H: 4.24; N: 7.68; Found: C: 49.44; H: 4.01; N:7.52.

13.58: 6-Chloro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{14}N_2O_4PCl{+}0.5\ H_2O$: C: 49.81; H: 4.18; N: 7.74; Found: C: 49.63; H: 3.93; N: 7.60.

13.59: 5-Phosphonomethylenoxy-1,2,3,4,5,6-hexahydroazapino[1,2-a]benzimidazole. mp=152-156; Anal. Cald. for $C_{13}H_{17}N_2O_4P$ + H_2O + 0.75 HBr + 0.5 CH_3CO_2H: C: 41.52; H: 5.41; N: 6.92; Found: C: 41.34; H: 5.58; N: 6.48.

13.60: 1-Isobutyl-4,5-dimethyl-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{20}N_2O_4PCl$ + 0.5 H_2O: C: 52.12 H: 5.40 N: 7.15; Found: C: 52.38; H: 5.23; N: 6.54.

13.61: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 219-220°C Anal. Cald. for $C_{17}H_{18}N_2O_4PCl$ + 1.33 H_2O + 0.1 HBr: C:49.46; H: 4.99; N:6.79; Found: C:49.74; H:4.94 N:6.49.

13.62: 6,7-Dimethyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$: C: 58.62; H: 6.08; N: 8.04; Found: C: 58.78; H: 5.68; N: 7.79.

13.63: 5-Chloro-6,7-dimethyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{20}N_2O_4P$ + 0.25 H_2O + 0.2 HBr: C: 50.61; H:5.17; N: 6.94; Found: C: 50.58; H:4.84; N: 6.58.

13.64: 7-Bromo-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{15}N_2O_4PBrF$ + 0.25 H_2O; C: 42.73; H: 3.71; N: 6.64; Br: 18.95; Found. C:42.86; H: 3.52; N: 6.49; Br: 19.21.

13.65: 6-Chloro-1-(3-methoxyphenyl)-2-(2-phosphono-5-furanyl) benzimidazole. mp = 184-185° C. Anal. Cald. for $C_{18}H_{14}N_2O_5PCl$ + 1.75 H_2O; C: 49.56; H: 4.04; N: 6.42; Found. C: 49.43; H: 3.71; N: 6.28.

13.66: N-(Phosphonomethyl)benzimidazole-2-carboxamide. mp = 258-260°C. Anal. Cald. for $C_9H_{10}N_3O_4P$ + 0.15 AcOH; C: 42.28; H: 4.04; N: 15.91; Found. C: 42.60; H: 4.02; N: 15.70.

13.67: 1-Isobutyl-5-fluoro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp >250 °C (dec.); Anal. Cald. for $C_{15}H_{15}N_2O_4PBrF$+ 0.25H_2O: C: 42.73; H: 3.71; N: 6.64. Found: C: 42.86; H: 3.52; N: 6.49.

13.68: 1-Isobutyl-5-fluoro-6-nitro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 161-165 °C; Anal. Cald. for $C_{15}H_{14}N_3O_6PBrF$ + 0.25H_2O + 1.0CH_3CO_2H: C: 38.77; H: 3.54; N: 7.98. Found: C: 39.00; H: 3.49; N: 8.22.

13.69: 1-Isobutyl-5-fluoro-6-amino-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 208-211 °C; Anal. Cald. for $C_{15}H_{16}N_3O_4PBrF$ + 0.5H_2O + 0.5CH_3CO_2H: C: 40.78; H: 4.06; N: 8.92. Found: C: 41.18; H: 4.27; N: 8.59.

13.70: 1-Isobutyl-4-amino-5-chloro-6,7-dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_3O_4PCl$+ 0.2 H_2O: C: 49.32; H: 5.16; N: 10.15. Found: C: 49.36; H: 4.94; N: 9.81.

13.71: 1-Isobutyl-5,7-difluoro-6-N,N-dimethylamino-2-(2-phosphono-5-furanyl) benzimidazole. mp = 176-180 °C; Anal. Cald. for $C_{17}H_{20}N_3O_4PF_2$ + 1.0 H_2O + 1.25 Hbr + 0.25 $C_6H_5CH_3$: C: 41.59; H: 4.70; N: 7.76. Found: C: 41.74; H: 4.65; N: 7.39.

13.72: 1-Isobutyl-7-hydroxymethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{16}H_{19}N_2O_5P$ + $0.5H_2O$: C: 53.48; H: 5.61; N: 7.80. Found: C: 53.35; H: 5.34; N: 7.48.

13.73: 5-Fluoro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{11}H_7N_2O_4PBrF$ + 0.1 H_2O: C: 36.41; H: 2.00; N: 7.72. Found: C: 36.67; H: 2.28; N: 7.41.

13.74: 4-Nitro-5-fluoro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 218-223 °C (dec.); Anal. Cald. for $C_{11}H_6N_3O_6PF$ + 0.75 H_2O: C: 31.49; H: 1.80; N: 10.01. Found: C: 31.77; H: 2.19; N: 9.41.

13.75: 5-Fluoro-6-nitro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{11}H_6N_3O_6PBrF$ + 0.25 H_2O + 0.25 C_3H_6O: C: 38.77; H: 3.54; N: 7.98. Found: C: 39.00; H: 3.49; N: 8.22.

13.76: 1-Isobutyl-5-fluoro-6-acetamido-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 217-221 °C (dec.); Anal. Cald. for $C_{17}H_{18}N_3O_5PBrF$ + 1.0 H_2O: C: 41.48; H: 4.1; N: 8.54. Found: C: 41.90; H: 4.06; N: 8.08.

13.77: 1-Isobutyl-4-acetamido-5-fluoro-7-ethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{23}N_3O_5PF$ + 1.0 H_2O: C: 51.70; H: 5.71; N: 9.52. Found: C: 52.03; H: 5.56; N: 9.11

13.78: 1-Isobutyl-4-N,N-dimethylamino-5-fluoro-7-ethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{25}N_3O_4PF$ + 1.25 H_2O + 1.5 HBr + 0.33EtOAc: C: 41.91; H: 5.48; N: 7.22. Found: C: 42.09; H: 5.41; N: 6.65.

13.79: 1-Isobutyl-5-fluoro-6-N,N-dimethylamino-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 183-188 °C; Anal. Cald. for $C_{17}H_{20}N_3O_4PBrF$ + 0.33 H_2O: C: 43.78; H: 4.47; N: 9.01. Found: C: 43.96; H: 4.60; N: 8.56.

13.80: 5-Fluoro-6-chloro-7-ethyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 165-190 °C; Anal. Cald. for $C_{13}H_{11}N_2O_4PClF$ + 1.33 H_2O: C: 42.34; H: 3.74; N: 7.60. Found: C: 42.31; H: 3.64; N: 7.43.

13.81: 1-Isobutyl-4-ethyl-5-chloro-6-Fluoro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PClF$ + $0.33H_2O$ + 0.25 HBr: C: 47.80; H: 4.70; N: 6.56. Found: C: 47.82; H: 4.66; N: 6.25.

13.82: 4,5,6,7-Tetramethyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 202-206 °C; Anal. Cald. for $C_{15}H_{17}N_2O4P$ + $1.6H_2O$: C: 51.42; H: 5.85; N: 8.00. Found: C: 51.38; H: 5.75; N: 7.75.

13.83: 1-Isobutyl-4,5,6,7-tetramethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{25}N_2O_4P$ + $0.75H_2O$ + 0.25 HBr: C: 55.64; H: 6.57; N: 6.83. Found: C: 55.67; H: 6.49; N: 6.65.

13.84: 4,6-Dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{13}H_{13}N_2O_4P$ + $1.6H_2O$: C: 48.44; H: 5.11; N: 8.69. Found: C: 48.46; H: 5.08; N: 8.62.

13.85: 1-Isobutyl-4,6-dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$ + 1.0 H_2O. mp = 209-212 °C; C: 55.73; H: 6.33; N: 7.65. Found: C: 55.99; H: 6.21; N: 7.57.

13.86: N-(2-Phosphonomethylacetate)benzimidazole-2-carboxamide. Anal. Cald. for $C_{11}H_{12}N_3O_6P$ + $0.5H_2O$ + 0.25 HBr. mp = 215-218°C; C: 38.58; H: 3.90; N: 12.27; Found. C: 38.94; H: 4.18; N: 12.43.

13.87: 1-Isobutyl-5,7-dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$ + $0.75H_2O$. mp = 196-200 °C; C: 56.43; H: 6.27; N: 7.74. Found: C: 56.47; H: 6.09; N: 7.59.

13.88: 1-Cyclopropylmethyl-4,5,6,7-tetramethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{23}N_2O_4P$ + 1.25 H_2O. mp = 207-208 °C; C: 57.50; H: 6.48; N: 7.06. Found: C: 57.32; H: 6.52; N: 7.06.

13.89: 1-Ethyl-4,5-dimethyl-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{16}N_2O_4PCl$ + 1.0 H_2O. C: 48.33; H: 4.87; N: 7.52. Found: C: 48.04; H: 4.81; N: 7.32.

13.90: 1-(4-Bromobutyl)-4,5-dimethyl-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PClBr$. mp = 212-216 °C; C: 44.23; H: 4.15; N: 6.07. Found: C: 44.07; H: 4.26; N: 5.91.

13.91: 4,5-Dimethyl-6-chloro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{13}H_{11}N_2O_4PBrCl$ + 1.33 H_2O. C: 36.35; H:3.21; N: 6.52. Found: C: 36.32; H:3.05; N: 6.41.

13.92: 1-Isobutyl-4,5-dimethyl-6-chloro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PBrCl$. C: 44.23; H:4.15; N: 6.07. Found: C: 44.19; H:4.14; N: 5.88

13.93: 1-Isobutyl-6,7-dimethyl-5-chloro-4-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PBrCl$. mp = 195-201 °C; C: 43.38; H:4.28; N: 5.95. Found: C: 43.67; H:4.32; N: 5.54.

13.94: 1-(4-Aminobutyl)-5-chloro-2-(2-phosphono-5-furanyl) benzimidazole hydrochloric acid salt. Anal. Cald. for $C_{15}H_{18}N_3O4PCl_2$ + 1.5H_2O + 1.0 HCl. mp = 236-240 °C (dec.); C: 38.36; H:4.72; N: 8.95. Found: C: 38.13; H:4.64; N: 8.88

13.95: 1-(4-Aminobutyl)-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{17}N_3O_4PCl$ + 1.0 H_2O. mp = 250-252 °C (dec.); C: 46.46; H:4.94; N: 10.84. Found: C: 46.21; H:4.79; N: 10.62

13.96: 1-Isobutyl-4-methyl-5-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{16}H_{18}N_2O_4PCl$. mp = 193-196 °C; C: 48.19; H:5.39; N: 7.02. Found: C: 48.24; H:5.19; N: 6.85.

Synthesis benzimidazoles with ether linkers :

Example 14.

Preparation of 2-methyl-4-nitrobenzimidazole.

Step 1.

To a solution of 7.0 g (45.7 mmol) 3-nitro-1,2-phenylenediamine in 70 mL of dioxane was added 4.34 mL(46.0 mmol) acetic anhydride and the solution was refluxed overnight. The mixture was cooled to room temperature and the solvents were removed under reduced pressure. The resultant syrup was dissolved in 100 mL of dioxane and 100 mL of 2N sodium hydroxide and was heated to 100° C for 1 h. The reaction was then cooled, concentrated under reduced pressure, and was partitioned between water and ethyl acetate. The organic phase was evaporated to dryness and the solid was washed with water and was dried at 60 °C overnight to yield 7.1 g (40.1 mmol, 87.6 %) of a yellow powder.

Step 2.

Preparation of 1-ethyl-2-methyl-4-nitrobenzimidazole.

To a solution of 0.47 g (2.65 mmol) 2-methyl-4-nitrobenzimidazole, and 0.12 g (2.92 mmol) of sodium hydride in 10 mL of dry dimethylformamide was added 0.218 mL (2.92 mmol) bromoethane. The mixture was heated overnight at 65 °C. The mixture was cooled to room temperature and the solvents were removed under reduced pressure. The resultant syrup was partitioned between water and ethyl acetate. The organic phase was evaporated to dryness and the syrup chromatographed on silica to yield 0.31 g (1.51 mmol, 52%) of a yellow syrup.

Step 3.

Preparation of 1-ethyl-2-bromomethyl-4-nitrobenzimidazole.

To a solution of 0.216 g (1.05 mmol) 1-ethyl-2-methyl-4-nitrobenzimidazole, 50 mL carbon tetrachloride and 0.375 g (2.11 mmol) NBS, was added 50 mg of AIBN. The reaction mixture was heated to 90 °C for five hours and the solution was cooled to room temperature. The solution was concentrated under reduced pressure and the resulting oil was chromatographed on silica to yield 0.16 g (0.57 mmol, 54 %) of a light yellow oil.

Step 4.

Preparation of 1-ethyl-4-nitro-2-[diethyl(methoxymethyl)phosphonate]benzimidazole.

To a solution of 0.191 g (1.14 mmol) diethyl (hydroxymethyl)phosphonate, 0.07 g (1.71 mmol) sodium hydride and 10 mL tetrahydrofuran at 0 °C was added a solution of 0.161 g (0.57 mmol) 1-ethyl-2-bromomethyl-4-nitrobenzimidazole in 10 mL of tetrahydrofuran. The reaction was stirred for 10 minutes at 0 °C and quenched with aqueous saturated ammonium chloride. The reaction contents were concentrated and the resultant solution was partitioned between ethyl acetate and H_2O. The organic layer was separated and dried over sodium sulfate and the solvent was removed under reduced pressure. The resultant oil was chromatographed on silica with 50 % hexane/ethylacetate to yield 0.055 g (0.148 mmol, 26.3 %) of a clear oil.

Step 5.

Preparation of 1-ethyl-4-nitro-2-[3-phospho(methoxymethyl)]benzimidazole.

Followed the procedure given in the Example 12.

Step 6.

Preparation of 1-ethyl-4-amino-2-[3-phospho(methoxymethyl)]benzimidazole.

Followed the procedure given in the Example 9, Method A.

Example 15.

Preparation of 1-isobutyl-4-amino-5-fluoro-7-bromo-2-[3-phospho(methoxymethyl)]benzimidazole.

Step 1.

Synthesis of diethylphosphomethyl acetaldehyde dimethyl acetal ether:

To a solution of 1.0 mmol diethyl (hydroxymethyl)phosphonate, 1.5 mmol of sodium hydride in 2 mL DMF at 0 °C was added a solution of 1.2 mmol of bromoacetaldehyde dimethyl acetal. After 3 h. at room temperature the mixture was diluted with 5 mL of water and extracted with ether (4 x 15 mL). The combined ether layers were concentrated. The residue was chromatographed on a silica gel column eluting with hexane-ethyl acetate (8:1) to yield the product.

Step 2.

Preparation of 1-isobutyl-4-nitro-5-fluoro-7-bromo-2-[3-diethylphospho(methoxymethyl)]benzimidazole:

To a solution of 1.0 mmol of 2-nitro-3-fluoro-5-bromo-6-isobutylamineaniline and 2.0 mmol of diethylphosphomethyl acetaldehyde dimethyl acetal ether in 5 mL THF at 0 °C was added 0.5 mL of 10 % H_2SO_4 and the mixture was heated at 75 °C for 40 min. Solvent was removed under reduced pressure, diluted with water and extracted with EtOAc. The combined EtOAc layers were concentrated. The residue was chromatographed on a silica gel column yield the product.

Step 3.

Followed the procedure given in the Example 4, Method A Step 2.

Step 4.

Preparation of 1-isobutyl-4-amino-5-fluoro-7-bromo-2-[3-diethylphospho(methoxymethyl)]benzimidazole:

Followed the procedure given in the Example 9, Method B.

Step 5.

Followed the procedure given in the Example 12.

15.1: 4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(1-methoxymethyl-3-phosphono)benzimidazole. mp = 200-202 °C(dec.); Anal. Cald. for $C_{13}H_{18}N_3O_4FBrP$: C: 38.07; H: 4.42; N: 10.24. Found: C: 37.87; H: 4.36; N: 10.15.

Example 16.

Benzimidazole phenyl synthesis

Step 1.

Preparation of diethyl-O-formylphenyloxymethylphosphonate.

To a suspension of 1.0 mmol of salicylaldehyde and 1.5 mmol of K_2CO_3 in 3 mL of DMF was added 1.0 mmol of diethyl iodomethylphosphonate and the mixture was heated at 50 °C for 3 days. Extraction and chromatography gave the title compound as an oil.

Step 2.

Preparation of diethyl -2-(4-nitrobenzimidazole-2-yl)phenoxymethyl phosphonate.

A mixture of 1.0 mmol of diethyl-O-formylphenyloxymethyl phosphonate, 1.0 mmol of 3-nitro-1,2-phenylenediamine, and 1.5 mmol of $FeCl_3$ in 5 mL of ethanol was heated at 80 °C for 20 h. Extraction and chromatography gave the title compound. R_f = 0.4 in EtOAc.

Step 3.

Preparation of diethyl 2-(4-nitro-1-ethyl-benzimidazole-2-yl)phenoxymethylphosphonate.

Followed the procedure given in the Example 5, Method A.

Step 4.

Preparation of diethyl 2-(4-amino-1-ethyl-benzimidazole-2-yl)phenoxymethylphosphonate.

Followed the procedure given in the Example 9, Method A.

Step 5.

4-Amino-1-ethyl-2-[1-(2-phosphonomethyloxy)phenyl]benzimidazole.

Followed the procedure given in the Example 12.

Example 17.

Preparation of N-(Phosphonomethyl)benzimidazole-2-carboxamide

Step 1.

To a solution of 1,2-phenylenediamine (5 g, 46.2 mmol) in 100 mL of acetic acid was added trichloromethylacetamidate (8.97 g, 50.8 mmol).The reaction mixture was stirred for 2 h at room temparature. Precipitated solid was filtered and washed with water and dried. The solid was dissolved in 1N KOH solution and stirred for 1 h. The solution was acidified with 3N hydrochloric acid at 0° C until pH 4 and the solid formed was filtered and washed with water. The solid 6.7 g (90%) was dried to give a white powder.(*Eur. J. Med. Chem.*, 1993, *28*: 71)

Step 2.

To a solution of 1.0 g (6.17 mmol) benzimidazole-2-carboxylic acid in 20 mL methylene chloride was added 5 mL diisopropylethylamine and 0.94 g (6.79 mmol) of diethyl(aminomethyl)phosphonate followed by 4.5 g (9.25 mmol) of PyBOP. The reaction contents were stirred at room temperature for 4h, filtered and eluted through a pad of silica with ethyl acetate. The filtrate was evaporated under reduced pressure and was resuspended in a minimum amount of ethyl acetate. The resulting solid was filtered and dried to give 876 mg of a light yellow powder.

Step 3.

Diethylphosphonate hydrolysis was carried out as described in Example 13.

The following compound was prepared in this manner:

17.1: N-(Phosphonomethyl)benzimidazole-2-carboxamide. 250-260 °C (dec.); Anal. cald. for C9H10N3O4P + 0.15 AcOH: C: 42.28; H: 4.04; N: 15.91. Found: C: 42.60; H: 4.02; N: 15.70.

Example 18.

General procedure for the synthesis of acyloxyalkyl phosphonate esters.

Method A:

To a solution of 1 mmol phosphonic acid in 10 mL of DMF or CH_3CN and 3.0 mmol of Hunigs base or *N,N'*-dicyclohexyl-4-morpholinecarboxamidine was added 5.0 mmol of the appropriate alkylating agent (For 6-chloronicotinoyloxymethylchloride, 5-bromonicotinoyloxymethylchloride, benzoyloxymethylchloride, p-fluorophenylchloride,

thiophenecarbonyloxymethylchloride, 2-furoyloxymethylchloride, 3-furoyloxymethylchloride, benzoyloxymethylchloride see ref. US 527033, Oct., 9, 1991 , EP 143 601, June 5, 1985; Chem. Abstr. 104, 5589z, 1986; these chlorides were treated with NaI in CH_3CN to generate the corresponding iodides). The reaction contents were stirred for 2 h and the solvent was removed under reduced pressure. The resultant syrup was chromatographed on silica (ref. EP 0 481 214 A1; J. E. Starrett, et. al. *J. Med. Chem.* **1994** *37*, 1857.).

The following compounds were prepared in this manner:

18.1: 4-Amino-1-isobutyl-2-(5-furanyl-2-bisisobutyryloxymethyl phosphonate)benzimidazole. MF = $C_{23}H_{30}N_3O_8P$; Mass Cald. MH^+ = 508, Obs. MH^+ = 508. R_f = 0.5 in 1:1 EtOAc:Hexane.

18.2: 4-Amino-5,7-dichloro-1-isobutyl-2-(5-furanyl-2-bispivaloyloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{36}N_3O_8PCl_2$: C: 51.27; H: 5.74; N: 6.64; Found: C: 51.22; H: 5.50; N: 6.42.

18.3: 6-Chloro-1-isobutyl-2-(2-bis-pivaloyloxymethylphosphono furan-5-yl) benzimidazole. Anal. Cald. for $C_{27}H_{36}N_2O_8PCl$: C:55.62 H:6.22 N:4.80; C:55.93 H:6.23 N:4.66.

18.4: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bispivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{41}N_3O_8PF$: C: 57.14; H: 6.78; N: 6.89; Found: C: 57.08; H: 6.77; N: 6.70.

18.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis pivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{38}N_2O_8PCl$: C: 57.19; H: 6.29; N: 4.60; Found: C: 56.85; H: 6.31; N: 4.53

18.6: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-thionyl-2-bispivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{38}N_2O_7PSCl$: C: 55.72; H: 6.13; N: 4.48; Found: C: 56.03; H: 6.01; N: 4.46

18.7: 4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(1-methoxymethyl-3-bispivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{36}N_3O_8FBrP$: C: 47.03; H: 6.00; N: 6.58. Found: C: 47.15; H: 6.12; N: 6.31

18.8: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bisisobutyryloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{32}N_2O_8PCl$: C: 54.11; H: 5.81; N: 5.05; Found: C: 54.05; H: 5.72; N: 4.89

18.9: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-thionyl-2-bisbenzoylthiomethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_6PS_2Cl$: C: 58.19; H: 4.44; N: 4.11; Found: C: 58.00; H: 4.50; N: 3.99

18.10: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bisbenzoyloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$ + 0.3Et OAc: C: 59.55; H: 4.72; N: 4.31; Found: C: 59.95; H: 4.36; N: 3.90

18.11: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bisbenzoylthiomethyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_6PS_2Cl$ + 1.25 H_2O: C: 54.95; H: 4.54; N: 4.13; Found: C: 54.92; H: 4.20; N: 3.93

18.12: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-fluoro-benzoyloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{26}N_2O_8PS_2ClF_2$ + 0.2 CH_2Cl_2: C: 55.44; H: 3.94; N: 4.14; Found: C: 55.43; H: 3.88; N: 3.87

18.13: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(6-chloronicotinoyl) oxymethylphosphonate]benzimidazole. Anal. Cald. for $C_{29}H_{24}N_4O_8PCl_3$: C: 50.20; H: 3.49; N: 8.07; Found: C: 50.43; H: 3.32; N: 7.99

18.14: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(2-furanoyl)oxymethyl phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_{10}PCl$: C: 53.79; H: 4.01; N: 4.65; Found: C: 53.60; H: 4.23; N: 4.68

18.15: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(3-furanoyl)oxymethyl phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_{10}PCl$: C: 53.79; H: 4.01; N: 4.65; Found: C: 53.82; H: 4.08; N: 4.51

18.16: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(2-thiocarbonyl)oxymethyl phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_8PS_2Cl$ + 0.75 H_2O: C: 50.00; H: 3.96; N: 4.32; Found: C: 49.76; H: 3.94; N: 4.34

18.17: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(5-bromonicotinoyl) oxymethylphosphonate]benzimidazole. Anal. Cald. for $C_{29}H_{24}N_4O_8PClBr_2$ + 0.1 EtOAc + 1.6 H_2O:C: 43.04; H: 3.44; N: 6.83; Found: 43.28; H: 3.36; N: 6.46

Method B:

A suspension of 1 mmol of phosphonic acid in 5 mL of thionyl chloride was heated at reflux temperature for 4 h. The reaction mixture was cooled and evaporated to dryness. To the resulting residue was added a solution of 4 mmol of benzoylthioethanol (ref. Lefebvre, I. et al. *J. Med. Chem.* 38, 3941, 1995; Benzaria, S. et al. *J. Med. Chem.* 39, 4958, 1996) and 2.5 mmol pyridine in 3 mL of methylene chloride. After stirring at 25 °C for 4 h the reaction was subjected to work up and chromatography.

The following compounds were prepared in this manner:

18.18: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis(benzoylthioethylphosphonate) benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_6PS_2Cl$: C: 58.02; H: 4.72; N: 4.10; Found: C: 57.90; H: 4.72; N: 4.04

18.19: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-[5-furanyl-2-bis(benzoyloxy-3-butyl)phosphonate]benzimidazole. Anal. Cald. for $C_{39}H_{45}N_3O_8PF$ + 0.5 H_2O: C: 63.06; H: 6.24; N: 5.66; Found: C: 62.86; H: 6.13; N: 5.46

18.20: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis (benzoyloxy-3-butyl)phosphonate]benzimidazole. Anal. Cald. for $C_{39}H_{42}N_2O_8PCl$ + 1.0 H_2O: C: 62.36; H: 5.90; N: 3.73; Found: C: 62.32; H: 5.80; N: 3.65

18.21: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis(acetyloxyethylphosphonate) benzimidazole. Anal. Cald. for $C_{23}H_{28}N_2O_8PCl$ + 0.2 H_2O: C: 52.07; H: 5.40; N: 5.28; Found: C: 51.67; H: 5.40; N: 5.07

18.22: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl)-2-bisacetylthioethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{33}N_3O_6PFS_2$ + 0.2 CH_2Cl_2 + 0.1 $PhCH_3$; C: 50.84; H: 5.63; N: 6.87 Found: C:50.74; H: 5.54 N: 6.48.

Example 19.

General procedure for hydroxyethyldisulfidylethylphosphonate diester.

A suspension of 1 mmol of phosphonic acid in 5 mL of thionyl chloride was heated at reflux temperature for 4 h. The reaction mixture was cooled and evaporated to dryness. To the resulting residue was added a solution of 4 mmol of 2-hydroxyethyl disulfide and 2.5 mmol pyridine in 3 mL of methylene chloride. After stirring at 25 °C for 4 h the reaction was subjected to work up and chromatography.

The following compounds were prepared in this manner:

19.1: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bis(hydroxyethyldisulfidylethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{37}N_3O_6PFS_4$ + 0.7 H_2O; C: 45.06; H: 5.81; N: 6.31; Found: C: 45.24; H: 5.67; N: 5.93.

19.2: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis(hydroxyethyldisulfidylethylphosphonate)benzimidazole. Anal. Cald. for

$C_{23}H_{32}N_2O_6PClS_4$ + 0.5 H_2O: C: 43.42; H: 5.23; N: 4.40; Found: C: 43.12; H: 4.94; N: 4.26.

Example 20.

General procedure for substituted-benzyl phosphonate diesters.

Followed the same procedure as in Example 18, Method B.

The following compounds were prepared in this manner:

20.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p*-chlorobenzylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_4PCl_3$ + 0.25 H_2O: C: 58.69; H: 4.53; N: 4.42; Found: C: 58.48; H: 4.62; N: 4.19

20.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p*-acetoxybenzylphosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{34}N_2O_8PCl$: C: 62.09; H: 5.06; N: 4.14; Found: C: 61.69; H: 4.93; N: 4.10

20.3: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-dimethoxybenzylphosphonate)benzimidazole. Anal. Cald. for $C_{37}H_{40}N_2O_{12}PCl$ + $0.4C_6H_5CH_3$: C: 59.16; H: 5.39; N: 3.47; Found: C: 59.19; H: 5.16; N: 3.34

20.4: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-methylbenzyl phosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{36}N_2O_8PCl$ + 2.0 H_2O + $0.5C_6H_5CH_3$: C: 60.75; H: 5.83; N: 3.68; Found: C: 60.82; H: 5.55; N: 3.32

20.5: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-methoxybenzyl phosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{36}N_2O_{10}PCl$ + 1.2 H_2O: C: 57.37; H: 5.28; N: 3.82; Found: C: 57.44; H: 5.16; N: 3.60

20.6: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-chlorobenzyl phosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_8PCl_3$: C: 55.06; H: 4.20; N: 3.89; Found: C: 54.76; H: 4.33; N: 3.64

20.7: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-benzylphosphonate) benzimidazole. Anal. Cald. for $C_{29}H_{28}N_2O_4PCl$: C: 62.99; H: 5.47; N: 5.07; Found: C: 62.76; H: 5.84; N: 5.20

20.8: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p,m*-diacetoxybenzylphosphonate)benzimidazole. Anal. Cald. for $C_{37}H_{36}N_2O_{12}PCl$ + 0.5 H_2O: C: 57.26; H: 4.81; N: 3.61; Found: C: 57.02; H: 4.84; N: 3.52.

Example 21.

General procedure for phenyl phosphonate diesters.

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

21.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-(5,6,7,8-tertahydro-2-napthyl)phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{38}N_2O_4PCl$: C: 69.31; H: 5.97; N: 4.37; Found: C: 69.33; H: 6.07; N: 4.14

21.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-phenyl phosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{26}N_2O_4PCl$: C: 64.63; H: 4.99; N: 5.20; Found: C: 64.58; H: 4.99; N: 5.21

21.3: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*o*-ethoxyphenylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{34}N_2O_6PCl$ + 0.67 H_2O: C: 62.60; H: 5.63; N: 4.42; Found: C: 62.57; H: 5.80; N: 4.24

21.4: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-mono-*o*-ethoxyphenylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{26}N_2O_5PCl$ + 1.5 H_2O + 0.1HCl: C: 56.49; H: 5.52; N: 5.27; Found: C: 56.22; H: 5.24; N: 5.01

21.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*o*-methoxyphenylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{30}N_2O_6PCl$: C: 62.79; H: 5.10; N: 4.72; Found: C: 62.79; H: 5.30; N: 4.54

21.6: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-phenyl phosphonate) benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_4PCl$ + 0.5H_2O: C: 62.86; H: 4.88; N: 5.43; Found: C: 62.72; H: 4.75; N: 5.54

21.7: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*o*-acetoxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$: C: 59.77; H: 4.53; N: 4.50; Found: C: 59.33; H: 4.82; N: 4.21

21.8: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$: C: 59.77; H: 4.53; N: 4.50; Found: C: 59.46; H: 4.67; N: 4.34

21.9: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-*p*-(4-morpholino)phenyl phosphonate]benzimidazole. Anal. Cald. for $C_{35}H_{38}N_4O_6PCl$ + 0.5 H_2O: C: 61.27; H: 5.73; N: 8.17; Found: C: 61.62; H: 5.78; N: 7.79

21.10: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-hydroxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_6PCl$ + 0.75 H_2O: C: 58.70; H: 4.65; N: 5.07; Found: C: 58.54; H: 4.43; N: 4.78

21.11: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*m*-acetoxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$ + 0.4 H_2O: C: 59.08; H: 4.61; N: 4.45; Found: C: 58.82; H: 4.54; N: 4.20

21.12: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(1-triozolo)acetoxyphenyl phosphonate]benzimidazole. Mass. Cald. for $C_{31}H_{26}N_8O_4PCl$: 641(M + H); Found: 641(M + H)

21.13: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-*m*-(*N,N*-dimethylamino) phenylphosphonate]benzimidazole. Anal. Cald. for $C_{31}H_{34}N_4O_4PCl$ + 1.5 H_2O + 0.35 CH_2Cl_2: C: 57.95; H: 5.85; N: 8.62; Found: C: 57.94; H: 5.49; N: 8.24

21.14: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetamidophenyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{30}N_4O_6PCl$ + 0.5 H_2O: C: 59.10; H: 4.96; N: 8.89; Found: C: 59.03; H: 5.23; N: 9.68

21.15: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bis(2-methylphenylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{33}N_3O_4PF$ + 0.7 H_2O; C: 64.84; H: 6.04; N: 7.32; Found: C: 64.88; H: 6.12; N: 7.10.

21.16: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bis(phenylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{29}N_3O_4PF$ + 0.3 H_2O; C: 64.63; H: 5.54; N: 7.80; Found: C: 64.61; H: 5.57; N: 7.47.

Example 22.

Preparation of (5-substituted 2-oxo-1,3-dioxolen-4-yl)methyl phosphonate prodrugs.

A solution of 1 mmol phosphonic acid in DMF and 2 mmol of sodium hydride was treated with 4 mmol of 5-substituted-4-bromomethyl-2-oxo-1,3-dioxolene (prepared according to *Chem. Pharm. Bull.* **1984**, *32(6)*, 2241.) at 25 °C for 24 h. Extraction and chromatography gave the phosphonate prodrug. The following compound was prepared in this manner:

22.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methylphosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{26}N_2O_{10}PCl$ + 0.75 H_2O: C: 62.79; H: 5.10; N: 4.72; Found: C: 62.79; H: 5.30; N: 4.54

Example 23.

General procedure for the synthesis of alkyloxycarbonyloxyalkyl phosphonate esters.

To a solution of 1 mmol phosphonic acid in 5 mL of anhydrous DMF was added 5 mmol of *N,N'*-dicyclohexyl-4-morpholinecarboxamidine followed by 5 mmol of isopropyloxycarbonyloxymethyliodide (all the alkyl and aryloxy(thio)carbonyloxymethyl iodides were prepared from the commercially available chloromethyl chloroformate according to the reported procedure, Tatsuo Nishimura et al. *J. Antibiotics*, **1987**, 40(1), 81-90). The reaction contents were stirred for 24 h at room temperature and the solvent was removed

under reduced pressure. The resultant syrup was chromatographed on silica with 50% EtOAc/Hexanes to yield the required product.

The following compounds were prepared in this manner:

23.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-biscyclohexyloxycarbonyloxymethylphosphonate)benzimidazole. mp = 120-122 °C; Anal. Cald. for $C_{33}H_{42}N_2O_{10}PCl$: C: 57.18; H: 6.11; N: 4.04; Found: C: 57.16; H: 6.13; N: 3.99

23.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisethyloxycarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{32}N_2O_{10}PCl$: C: 51.16; H: 5.50; N: 4.77; Found: C: 51.06; H: 5.30; N: 4.72

23.3: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisisopropyloxycarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{34}N_2O_{10}PCl$: C: 52.90; H: 5.59; N: 4.57; Found: C: 52.96; H: 5.56; N: 4.49

23.4: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisisopropylthiocarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{34}N_2O_8PClS_2$: C: 50.27; H: 5.31; N: 4.34; Found: C: 49.99; H: 5.35; N: 4.27

23.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisphenylthiocarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_8PClS_2$: C: 55.58; H: 4.24; N: 3.93; Found: C: 55.36; H: 4.43; N: 3.77

23.6: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisphenyloxy carbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_{10}PCl$ + 0.5 H_2O: C: 55.58; H: 4.24; N: 3.93; Found: C: 55.36; H: 4.43; N: 3.77

23.7: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bismethyloxy carbonyloxymethylphosphonate)benzimidazole. mp = 87-85 °C; Anal. Cald. for $C_{33}H_{30}N_2O_8PClS_2$: C: 55.58; H: 4.24; N: 3.93; Found: C: 55.36; H: 4.43; N: 3.77

23.8: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bisethyloxy carbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{33}N_3O_{10}FP$: C: 51.28; H: 5.68; N: 7.18. Found: 51.51; H: 5.83; N: 7.18

23.9: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-methoxyphenyloxy carbonyl oxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{12}PCl$: C: 55.43; H: 4.51; N: 3.92; Found: C: 55.52; H: 4.56; N: 3.47

23.10: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*o*-methoxyphenyloxycarbonyloxy methylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{12}PCl$: C: 55.43; H: 4.51; N: 3.92; Found: C: 55.34; H: 4.62; N: 3.66

23.11: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*m*-methoxyphenyloxycarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{12}PCl$: C: 55.43; H: 4.51; N: 3.92; Found: C: 55.28; H: 4.68; N: 3.83

23.12: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*o*-methylphenyloxycarbonyl oxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{10}PCl$: C: 58.03; H: 4.72; N: 4.10; Found: C: 57.78; H: 4.60; N: 3.89

23.13: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-chlorophenyloxycarbonyl oxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{26}N_2O_{10}PCl_3$: C: 51.44; H: 3.62; N: 3.87; Found: C: 51.46; H: 3.86; N: 3.81

23.14: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-1,4-biphenyloxycarbonyl oxymethylphosphonate)benzimidazole. mp = 112-114 °C; Anal. Cald. for $C_{43}H_{36}N_2O_{10}PCl$: C: 63.98; H: 4.50; N: 3.47; Found: C: 63.90; H: 4.39; N: 3.38

23.15: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-phthalylethyloxycarbonyloxy methylphosphonate)benzimidazole. mp = 112-114 °C; Anal. Cald. for $C_{43}H_{36}N_2O_{10}PCl$: C: 63.98; H: 4.50; N: 3.47; Found: C: 63.90; H: 4.39; N: 3.38

23.16: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(*N*-Phenyl, *N*-methylcarbamoyl) oxymethylphosphonate]benzimidazole. Anal. Cald. for $C_{33}H_{34}N_4O_8PCl$ + 0.25 HI + 0.66 H_2O: C: 54.67; H: 4.95; N: 7.73; Found: 54.71; H: 4.76; N: 7.44

23.17: 6-Chloro-1-isobutyl-2-[5-furanyl-2-mono-(4-morpholinocarbonyloxy methyl)phosphonate]benzimidazole. Anal. Cald. for $C_{21}H_{25}N_3O_7PCl$ + 0.5 HI + 0.25 H_2O: C: 44.54; H: 4.63; N: 7.42; Found: 44.59; H: 4.52; N: 7.56

Example 24.

General procedure for the substituted-ethyl phosphonate diesters.

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

24.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-(2-trichloroethyl)phosphonate]benzimidazole. mp = 132-134 °C; Anal. Cald. for $C_{21}H_{20}N_2O_4PCl_7$: C: 39.19; H: 3.13; N: 4.35; Found: C: 39.37; H: 3.28; N: 4.18

24.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-(2-bromoethyl)phosphonate]benzimidazole. Anal. Cald. for $C_{21}H_{24}N_2O_4PClBr_2$: C: 42.42; H: 4.07; N: 4.71; Found: C: 42.64; H: 4.35; N: 4.65

24.3: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(2-azidoethyl)phosphonate] benzimidazole. mp = 73-75 °C; Anal. Cald. for $C_{19}H_{22}N_8O_4PCl$: C: 46.30; H: 4.50; N: 22.74; Found: C: 46.30; H: 4.39; N: 22.51

The azido compound (**24.3**) was obtained by reaction of the compound 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(2-iodoethyl)phosphonate]benzimidazole and sodium azide in DMF.

24.4: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(2-aminoethyl)phosphonate] benzimidazole hydrogen chloride salt. mp = 160 °C; Anal. Cald. for $C_{19}H_{26}N_4O_4PCl.3HCl + 1.0\ H_2O$: C: 40.16; H: 5.50; N: 9.80; Found: C: 39.88; H: 5.41; N: 9.43

The amino compound (**24.4**) was obtained by the hydrogenation of the azido compound (**24.3**) in presence of 10 % Pd/C and HCl in EtOAc.

24.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis(2-iodoethyl)phosphonate]benzimidazole. Anal. Cald. for $C_{21}H_{24}N_2O_4PClI_2$: C: 34.44; H: 3.35; N: 4.23; Found: C: 34.69; H: 3.12; N: 4.01.

24.6: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(2-*N,N*-dimethylaminoethyl)phosphonate]benzimidazole hydrogen chloride salt. mp = 61-63° C; Anal. Cald. for $C_{23}H_{34}N_4O_4PCl$: C: 55.59; H: 6.90; N: 11.27; Found: C: 55.34; H: 7.06; N: 11.07.

Example 25.

General procedure for the synthesis of phosphonoamidates. (ref. Starret, J. E. et al. *J. Med. Chem.* 37, 1857, **1994**).

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

25.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-cyclic (2,2-dimethylpropyl)phosphonoamidate]benzimidazole. mp = 132-134 °C; Anal. Cald. for $C_{21}H_{20}N_2O_4PCl_7$: C: 39.19; H: 3.13; N: 4.35; Found: C: 39.37; H: 3.28; N: 4.18

Example 26.

General procedure for the synthesis of substituted amidoalkyl esters. (ref. Starret, J. E. et al. *J. Med. Chem.* 37, 1857, **1994**).

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

26.1: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-{*N,N*(2-hydroxyethyl)amido methyl} phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{38}N_4O_{10}PCl$ + 0.4 CH_2Cl_2 + 1.0 MeOH: C: 47.97; H: 6.07; N: 7.88; Found: C: 47.69; H: 5.88; N: 7.53

Example 27.

General procedure for the synthesis of alkyloxycarbonylalkyl esters. (ref. Serafinowska, H. T., et. al. *J. Med. Chem.* **1995** *38*, 1372).

Followed the same procedure as in Example 18, Method A

The following compounds were prepared in this manner:

27.1: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bismethyloxycarbonylmethyl phosphonate)benzimidazole. Anal. Cald. for $C_{21}H_{24}N_2O_8PCl$ + 1.0 H_2O: C: 50.56; H: 4.85; N: 5.62; Found: C: 50.53; H: 5.02; N: 5.56

Example 28.

General procedure for the synthesis of substituted-phenylalkyl esters.

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

28.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisphenpropylphosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{38}N_2O_4PCl$: C: 68.12; H: 6.21; N: 4.54; Found: C: 67.87; H: 6.32; N: 4.49

28.2: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p*-acetoxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{40}N_2O_8PCl$ + 0.2 H_2O: C: 62.53; H: 5.73; N: 3.94; Found: C: 62.14; H: 5.67; N: 3.88

28.3: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(3-phenyl-3-acetoxypropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{34}H_{40}N_2O_8PCl$ + 1.85 H_2O: C: 62.02; H: 5.95; N: 3.78; Found: C: 59.63; H: 6.14; N: 3.55

28.4: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p*-hydroxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{33}H_{36}N_2O_6PCl$ + 0.08 H_2O: C: 63.48; H: 5.84; N: 4.49; Found: C: 63.05; H: 5.69; N: 4.32

28.5: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p*-methoxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{35}H_{40}N_2O_6PCl$: C: 64.56; H: 6.19; N: 4.30; Found: C: 64.20; H: 6.13; N: 4.08

28.6: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p,m*-dimethoxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{44}N_2O_0PCl$: C: 62.49; H: 6.24; N: 3.94; Found: C: 62.06; H: 6.02; N: 3.62

Example 29.

General procedure for the synthesis of substituted phthalimide esters.

To a solution of 1 mmol phosphonic acid in 10 mL of DMF or CH_3CN and 3.0 mmol of Hunigs base or *N,N'*-dicyclohexyl-4-morpholine carboxamidine is added 5.0 mmol of the substituted 3-bromophthalide. The reaction contents are stirred for 2 h and the solvent is removed under reduced pressure. The resultant syrup is chromatographed on silica(Clayton, J. P. et al. *J. Med. Chem.* **1976** *19*, 1385.).

Example 30:

General procedure for cyclic 1,3-cyclohexyl phosphonate diesters:

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

30.1: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-[1-hydroxy-3,5-cyclohexylphosphono-5-furanyl]benzimidazole. mp = 211 - 215°C; Anal. Cald. for $C_{23}H_{26}ClN_2O_5P + 2/3\ H_2O$: C: 56.50; H: 5.64; N: 5.73. Found: C: 56.65; H: 5.54 ; N: 5.64.

30.2: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-[1-acetylhydroxy-3,5-cyclohexylphosphono-5-furanyl]benzimidazole, minor isomer; Anal. Cald. for $C_{25}H_{28}ClN_2O_6P + 1.5\ H_2O$: C: 55.00 ; H: 5.72; N: 5.13. Found: C: 55.19; H: 5.31; N: 4.65.

30.3: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-[1-acetylhydroxy-3,5-cyclohexylphosphono-5-furanyl]benzimidazole, major isomer; Anal. Cald. for $C_{25}H_{28}ClN_2O_6P + 0.75\ H_20 + 0.1$ EtOAc: C: 56.37; H: 5.64; N: 5.18. Found: C: 56.68; H: 5.69; N: 4.80.

30.4: 6-Chloro-1-isobutyl-2-{2-[5-(1-hydroxy-3,5-cyclohexyl)phosphono] furanyl}benzimidazole, minor isomer. mp >220°C; Anal. Cald. for $C_{21}H_{24}ClN_2O_5P + 1/3\ H_2O$: C: 55.21; H: 5.44; N: 6.13. Found: C: 55.04; H: 5.50; N: 6.00.

30.5: 6-Chloro-1-isobutyl-2-{2-[5-(1-hydroxy-3,5-cyclohexyl)phosphono] furanyl}benzimidazole, major isomer. mp >220°C; Anal. Cald. for $C_{21}H_{24}ClN_2O_5P$: C: 55.94; H: 5.37; N: 6.21. Found: C: 55.73; H: 5.34; N: 6.13.

Example 31:

General procedure for the cyclic substituted 1,3-propyl phosphonate diesters:

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

31.1: 6-Chloro-1-isobutyl-2-(2-(5-(1-R-phenyl-1,3-propyl)phosphono)furanyl) benzimidazole, major isomer. mp = 204 - 206 °C; Anal. Cald. for $C_{24}H_{24}ClN_2O4P$: C: 61.22; H: 5.14; N: 5.95. Found: C: 60.95; H: 5.01; N: 5.88.

31.2: 6-Chloro-1-isobutyl-2-(2-(5-(1-R-phenyl-1,3-propyl)phosphono) furanyl)benzimidazole, minor isomer; Anal. Cald. for $C_{24}H_{24}ClN_2O_4P + H_2O$: C: 58.96; H: 5.36; N: 5.73. Found: C: 58.85; H: 5.48; N: 5.55.

The two diastereomers were separated by column chromatography by eluting with methanol-methylene chloride (5:95).

31.3: 6-Chloro-1-isobutyl-2-{5-[1S-(4-nitrophenyl)-2R-acetylamino-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, major isomer; MH^+ Cald. for $C_{26}H_{26}ClN_4O_7P$: 573.Found: 573.

31.4: 6-Chloro-1-isobutyl-2-{5-[1S-(4-nitrophenyl)-2R-acetylamino-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, minor isomer; Anal. Cald. for $C_{26}H_{26}ClN_4O_7P + 1.6\ H_2O + 0.25\ CH_2Cl_2$: C:50.61; H: 4.81; N: 8.99. Found: C: 50.25; H: 4.37; N: 9.01.

31.5: 6-Chloro-1-isobutyl-2-{5-[1S-(4-methylthiophenyl)-2S-acetylamino-propan-1,3-yl]phosphono-2-furanyl}benzimidazole; Anal. Cald. for $C_{27}H_{29}ClN_3O_5PS + 1\ H_2O + 0.35\ CH_2Cl_2$: C: 52.83; H: 5.14; N: 6.76. Found: C: 52.44; H: 4.76; N: 6.59 .

All three diastereomers were separated by column chromatography by eluting with methanol-methylene chloride (5:95). The substituted 1,3-diol to prepare **31.3, 31.4, 315** was made by the following method.

To a solution of D-threo-2-amino-1-(4-nitrophenyl)-1,3-propane diol (2.0 g, 9.4 mmol) in pyridine (20 mL) was added acetic anhydride (0.9 mL, 9.4 mmol) slowly at 0°C. The reaction was warmed to room temperature and allowed to stir for 1h. Reaction mixture was concentrated under reduced pressure and

azeotroped. Column chromatography by elution with ethyl acetate-methylene chloride (4:1) resulted in 1.7 g of pure acetylated product.

31.6: 6-Chloro-1-isobutyl-2-{5-[1-(2-pyridyl)-propan-1,3-yl] phosphono-2-furanyl}benzimidazole. Anal. Cald. for $C_{23}H_{23}ClN_3O_4P$ + 1.5 H_2O + 0.3 CH_2Cl_2: C: 53.37; H: 5.11; N: 8.01. Found: C: 53.23; H: 4.73 ; N: 7.69.

31.7: 6-Chloro-1-isobutyl-2-{5-[1-(N-oxo-2-pyridyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 195.0 °C (dec.); Anal. Cald. for $C_{23}H_{23}ClN_3O_5P$ + 0.25 H_2O + 0.25 CH_2Cl_2: C: 54.37; H: 4.71; N: 8.18. Found: C: 54.77; H: 4.86; N: 7.76.

31.8: 6-Chloro-1-isobutyl-2-{5-[1-(4-pyridyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 165.0 °C (dec.); Mass Cald. for $C_{23}H_{23}ClN_3O_4P$: MH^+ 454 : Found: MH^+ 454

The substituted 1,3-diol used to prepare **31.6, 31.8** were made by the following 2 step method.

Step A: (*J. Org. Chem.*, **1957**, 22, 589)

To a solution of 2-pyridinepropanol (10 g, 72.9 mmol) in acetic acid (75 mL) was added 30% hydrogen peroxide slowly. The reaction mixture was heated to 80 °C for 16 h. The reaction was concentrated under vacuum and the residue was dissolved in acetic anhydride (100 mL) and heated at 110 °C overnight. Acetic anhydride was evaporated upon completion of reaction. Chromatography of the mixture by eluting with methanol-methylene chloride (1:9) resulted in 10.5 g of pure diacetate.

Step B:

To a solution of diacetate (5 g, 21.1 mmol) in methanol-water (3:1, 40 mL) was added potassium carbonate (14.6 g, 105.5 mmol). After stirring for 3 h at room temperature, the reaction mixture was concentrated. The residue was chromatographed by eluting with methanol-methylene chloride (1:9) to give crystalline diol.

The compound **31.7** was prepared by the oxidation of the compound **31.6** by the following method.

To a solution of 6-chloro-1-isobutyl-2-{5-[1-(2-pyridyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole (172 mg, 0.36 mmol) in methylene chloride was added 3-chloroperoxybenzoic acid (252 mg, 0.72 mmol) at 0°C. The reaction was warmed to room temperature and allowed stir for 3h. The

solvent was evaporated under reduced pressure. Chromatography by elution with methanol-methylenecchloride (5:95) resulted in 100 mg of pure N-oxide.

31.9: 6-Chloro-1-isobutyl-2-{5-[1-(4-fluorophenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 207 - 208 °C; Anal. Cald. for $C_{24}H_{23}ClFN_2O_4P$: C: 58.96; H: 4.74; N: 5.73. Found: C: 59.20; H: 4.64; N: 5.59.

31.10: 6-Chloro-1-isobutyl-2-{5-[1-(4-fluorophenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 176 - 179°C; Anal. Cald. for $C_{24}H_{23}ClFN_2O_4P$ + 0.5H_2O: C: 57.90; H: 4.86; N: 5.63. Found: C: 57.60; H: 4.68; N: 5.54.

The substituted 1,3-diol used to prepare **31.9, 31.10** was made by the following 3 step method.

<u>StepA:</u> (*J. Org. Chem.*, **1988**, 53, 911)

To a solution of oxalyl chloride (5.7 mL, 97 mmol) in dichloromethane (200 mL) at -78°C was added dimethyl sulfoxide (9.2 mL, 130 mmol). The reaction mixture was stirred at -78° C for 20 min. before addition of 3-(benzyloxy)propan-1-ol (11 g, 65 mmol) in dichloromethane (25 mL). After an hour at -78°C, reaction was quenched with triethylamine (19 mL, 260 mmol) and warmed to room temperature. Work-up and column chromatography by elution with dichloromethane resulted in 8 g of 3-(benzyloxy)propan-1-al.

<u>Step B:</u>

To a solution of 3-(benzyloxy)propan-1-al (1 g, 6.1 mmol) in THF at 0° C was added a 1M solution of 4-fluorophenylmagnesium bromide in THF (6.7 mL, 6.7 mmol). The reaction was warmed to room temperature and stirred for 1 h. Work-up and column chromatography by elution with dichloromethane resulted in 0.7 g of alcohol.

<u>Step C:</u>

To a solution of benzyl ether (500 mg) in ethyl acetate (10 mL) was added 10%$Pd(OH)_2$-C (100 mg). The reaction was stirred under a hydrogen atmosphere for 16 h. The reaction mixture was filtered through Celite and concentrated. Chromatography of the residue by elution with ethyl acetate-dichloromethane (1:1) resulted in 340 mg of product.

31.11: 6-Chloro-1-isobutyl-2-{5-[1-(3-bromo-4-methoxyphenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, major isomer. mp = 167 - 169 °C; Anal. Cald. for $C_{25}H_{25}BrClN_2O_5P$: C: 51.79; H: 4.35; N: 4.83. Found: C: 51.77; H: 4.25; N: 4.73.

31.12: 6-Chloro-1-isobutyl-2-{5-[1-(3-Bromo-4-methoxyphenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, minor isomer. Anal. Cald. for $C_{25}H_{25}BrClN_2O_5P$ + $0.55CHCl_3$: C: 47.54; H: 3.99; N: 4.34. Found: C: 47.50; H: 3.89; N: 3.99.

The substituted 1,3-diol to prepare **31.11, 31.12** was made by the following 2 step method.

Step A: (*J. Org. Chem.*, **1990**, 55, 4744)

To a solution of diisopropylamine (4.1 mL, 29.4 mmol) in ether (40 mL) at -78 °C was added 2.5M n-butyl lithium (11.8 mL, 29.4 mmol). The reaction was stirred for 15 min before adding t-butyl acetate (4 mL, 29.4 mmol) in ether (10 mL). After 20 min, aldehyde (3g, 14 mmol) in ether (10 mL) was added and warmed to room temperature where it was stirred for 16 h. Work-up and column chromatography by elution with ethyl acetate-dichloromethane (1:9) resulted in 3.3 g of addition product.

Step B:

To a solution of t-butyl ester (1.5 g, 4.5 mmol) in THF (20 mL) was added 1M lithium aluminum hydride at 0° C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with ethyl acetate and saturated aq. sodium sulfate was added to precipitate the salts. Filtration and concentration of solvent resulted in crude diol. Column chromatography by elution with ethyl acetate-dichloromethane (1:1) gave 970 mg of pure diol.

31.13: 6-Chloro-1-isobutyl-2-{5-[2-(hydroxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 164 - 165 °C; Anal. Cald. for $C_{19}H_{22}ClN_2O_5P$: C: 53.72; H: 5.22; N: 6.59. Found: C: 53.62; H: 5.18; N: 6.42.

31.14: 6-Chloro-1-isobutyl-2-{5-[2-(acetoxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 132 - 134 °C; Anal. Cald. for $C_{21}H_{24}ClN_2O_6P$: C: 54.03; H: 5.18; N: 6.00 . Found: C: 54.17; H: 4.99 ; N: 5.81.

31.15: 6-Chloro-1-isobutyl-2-{5-[2-(methoxycarbonyloxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 138 - 140 °C; Anal. Cald. for $C_{21}H_{24}ClN_2O_7P$: C: 52.24; H: 5.01; N: 5.80. Found: C: 52.13; H: 5.07; N: 5.51.

31.16: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-{5-[2-(acetoxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole; Anal. Cald. for $C_{23}H_{29}FN_3O_6P$ + 0.3 H_2O: C: 55.38; H: 5.98; N: 8.42. Found: C: 55.60; H: 6.31; N: 8.02.

31.17: 6-Amino-9-neopentyl-8-{5-[2-(acetoxymethyl)-propan-1,3 -yl]phosphono-2-furanyl}purine. mp = 164 - 165 °C; Anal. Cald. for

$C_{20}H_{26}N_5O_6P$: C: 51.84; H: 5.65; N: 15.11 . Found: C: 52.12; H: 5.77 ; N: 14.59.

31.18: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-{5-[2-(cyclohexylcarbonyloxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 60-63° C; Anal. Cald. for $C_{28}H_{37}FN_3O_6P$: C: 59.89; H: 6.64; N: 7.48. Found: C: 59.97; H: 6.60; N: 7.33.

31.19: 6-Chloro-1-isobutyl-2-{5-[2-(aminomethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 158 - 160° C; Anal. Cald. for $C_{19}H_{23}ClN_3O_4P$: C: 51.13; H: 5.76; N: 9.41. Found: C: 51.35; H: 5.48; N: 9.05.

The substituted 1,3-diol to prepare **31.16** was made by the following method.

Monoacetylation of 2-(hydroxymethyl)-1,3-propanediol:

To a solution of 2-(hydroxymethyl)-1,3-propanediol (1 g, 9.4 mmol) in pyridine (7.5 mL) at 0° C was added acetic anhydride (0.89 mL, 9.4 mmol) slowly. The resulting solution was warmed to room temperature and stirred for 16 h. The reaction was concentrated under reduced pressure and chromatographed by eluting with methanol-dichloromethane (1:9) to give 510 mg of pure acetate.

The substituted 1,3-diol to prepare **31.17** was made by the following method.

Methyl carbonate formation of 2-(hydroxymethyl)-1,3-propanediol:

To a solution of 2-(hydroxymethyl)-1,3-propanediol (1 g, 9.4 mmol) in dichloromethane (20 mL) and pyridine (7.5 mL) at 0° C was added methyl chloroformate (0.79 mL, 9.4 mmol) slowly. The resulting solution was warmed to room temperature and stirred for 16 h. The reaction was concentrated under reduced pressure and chromatographed by eluting with methanol-dichloromethane (1:4) to give 650 mg of pure carbonate.

Example 32.

General procedure for 2-(3-phthalidyl)ethyl phosphonate diesters:

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

32.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-2-(3-phthalidylethyl)phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{34}N_2O_8PCl$ + 1.2 H_2O: C: 61.49; H: 5.08; N: 3.88; Found: C: 61.29; H: 4.89; N: 3.72

2-(3-phthalidyl)ethanol was prepared by the following method.

A solution of phthalide-3-acetic acid (1 mmol) in THF was treated with borane dimethylsulfide (1.5 mmol) at 0 °C for 1h, and 25 °C for 24 h. Extraction and chromatography gave 2-(3-phthalidyl)ethanol as a light yellow oil. TLC: R_f = 0.25, 50% EtOAc - hexane.

Example 33.

Preparation of benzimidazole phosphonate amine salts

A mixture of 1-cyclopropanemethyl-6-chloro-4,5-dimethyl-2-(2-(5-phosphono)furanyl)benzimidazole (1 mmol) and tris(hydroxymethyl)aminomethane (1.05 mmol) in methanol was stirred at 25 °C for 24 h. Evaporation of the solvent gave the salt as an yellow solid.

33.1: 1-cyclopropanemethyl-6-chloro-4,5-dimethyl-2-(2-(5-phosphono)furanyl)benzimidazole tris(hydroxymethyl)aminomethane. mp 175-178 °C; Anal. calcd. for $C_{21}H_{29}N_3O_7PCl$ + 2.3 H_2O: C: 46.42; H: 6.23; N: 7.73. Found: C: 46.16; H: 6.22; N: 7.98.

Examples of use of the method of the invention includes the following. It will be understood that these examples are exemplary and that the method of the invention is not limited solely to these examples.

For the purposes of clarity and brevity, chemical compounds are referred to by synthetic Example number in the biological examples below.

Besides the following Examples, assays that may be useful for identifying compounds which inhibit gluconeogenesis include the following animal models of diabetes:

i. Animals with pancreatic b-cells destroyed by specific chemical cytotoxins such as Alloxan or Streptozotocin (e.g. the Streptozotocin-treated mouse, -rat, dog, and -monkey). Kodama, H., Fujita, M., Yamaguchi, I., Japanese Journal of Pharmacology 66, 331-336 (1994) (mouse); Youn, J.H., Kim, J.K., Buchanan, T.A., Diabetes 43, 564-571 (1994) (rat); Le Marchand, Y., Loten, E.G., Assimacopoulos-Jannet, F., et al., Diabetes 27, 1182-88 (1978) (dog); and Pitkin, R.M., Reynolds, W.A., Diabetes 19, 70-85 (1970) (monkey).

ii. Mutant mice such as the C57BL/Ks db/db, C57BL/Ks ob/ob, and C57BL/6J ob/ob strains from Jackson Laboratory, Bar Harbor, and others such as Yellow Obese, T-KK, and New Zealand Obese. Coleman, D.L., Hummel, K.P., Diabetologia 3, 238-248 (1967) (C57BL/Ks db/db); Coleman, D.L., Diabetologia 14, 141-148 (1978) (C57BL/6J ob/ob); Wolff, G.L., Pitot, H.C.,

Genetics 73, 109-123 (1973) (Yellow Obese); Dulin, W.E., Wyse, B.M., Diabetologia 6, 317-323 (1970) (T-KK); and Bielschowsky, M., Bielschowsky, F. Proceedings of the University of Otago Medical School 31, 29-31 (1953) (New Zealand Obese).

iii. Mutant rats such as the Zucker fa/fa Rat rendered diabetic with Streptozotocin or Dexamethasone, the Zucker Diabetic Fatty Rat, and the Wistar Kyoto Fatty Rat. Stolz, K.J., Martin, R.J. Journal of Nutrition 112, 997-1002 (1982) (Streptozotocin); Ogawa, A., Johnson, J.H., Ohnbeda, M., McAllister, C.T., Inman, L., Alam, T., Unger, R.H., The Journal of Clinical Investigation 90, 497-504 (1992) (Dexamethasone); Clark, J.B., Palmer, C.J., Shaw, W.N., Proceedings of the Society for Experimental Biology and Medicine 173, 68-75 (1983) (Zucker Diabetic Fatty Rat); and Idida, H., Shino, A., Matsuo, T., et al., Diabetes 30, 1045-1050 (1981) (Wistar Kyoto Fatty Rat).

iv. Animals with spontaneous diabetes such as the Chinese Hamster, the Guinea Pig, the New Zealand White Rabbit, and non-human primates such as the Rhesus monkey and Squirrel monkey. Gerritsen, G.C., Connel, M.A., Blanks, M.C., Proceedings of the Nutrition Society 40, 237 245 (1981) (Chinese Hamster); Lang, C.M., Munger, B.L., Diabetes 25, 434-443 (1976) (Guinea Pig); Conaway, H.H., Brown, C.J., Sanders, L.L. eta l., Journal of Heredity 71, 179-186 (1980) (New Zealand White Rabbit); Hansen, B.C., Bodkin, M.L., Diabetologia 29, 713-719 (1986) (Rhesus monkey); and Davidson, I.W., Lang, C.M., Blackwell, W.L., Diabetes 16,395-401 (1967) (Squirrel monkey).

v. Animals with nutritionally induced diabetes such as the Sand Rat, the Spiny Mouse, the Mongolian Gerbil, and the Cohen Sucrose-Induced Diabetic Rat. Schmidt-Nielsen, K., Hainess, H.B., Hackel, D.B., Science 143, 689-690 (1964) (Sand Rat); Gonet, A.E., Stauffacher, W., Pictet, R., et al., Diabetologia 1, 162-171 (1965) (Spiny Mouse); Boquist, L., Diabetologia 8, 274-282 (1972) (Mongolian Gerbil); and Cohen, A.M., Teitebaum, A., Saliternik, R., Metabolism 21, 235-240 (1972) (Cohen Sucrose-Induced Diabetic Rat).

vi. Any other animal with one of the following or a combination of the following characteristics resulting from a genetic predisposition, genetic engineering, selective breeding, or chemical or nutritional induction: impaired glucose tolerance, insulin resistance, hyperglycemia, obesity, accelerated gluconeogenesis, increased hepatic glucose output.

BIOLOGICAL EXAMPLES

Example A: Inhibition of Human Liver FBPase

E. coli strain BL21 transformed with a human liver FBPase-encoding plasmid was obtained from Dr. M. R. El-Maghrabi at the State University of New York at Stony Brook. hlFBPase was typically purified from 10 liters of *E. coli* culture as described (M. Gidh-Jain et al. ,1994, *The Journal of Biological Chemistry* 269, pp 27732-27738). Enzymatic activity was measured spectrophotometrically in reactions that coupled the formation of product (fructose 6-phosphate) to the reduction of dimethylthiazoldiphenyltetrazolium bromide (MTT) via NADP and phenazine methosulfate (PMS) , using phosphoglucose isomerase and glucose 6-phosphate dehydrogenase as the coupling enzymes. Reaction mixtures (200 µl) were made up in 96-well microtitre plates, and consisted of 50 mM Tris-HCl, pH 7.4, 100 mM KCl, 5 mM EGTA, 2 mM MgCl2, 0.2 mM NADP, 1 mg/ml BSA, 1 mM MTT, 0.6 mM PMS, 1 unit/mL phosphoglucose isomerase, 2 units/mL glucose 6-phosphate dehydrogenase, and 0.150 mM substrate (fructose 1,6-bisphosphate). Inhibitor concentrations were varied from 0.01 µM to 10 µM. Reactions were started by the addition of 0.002 units of pure hlFBPase and were monitored for 7 minutes at 590 nm in a Molecular Devices Plate Reader (37°C).

Figure 2 shows the concentration-dependent inhibitory activity of compounds **12.61**, **12.53**, **12.52**, and **12.64**.

Table 2 below provides the IC_{50} values for several compounds prepared in Examples 12 and 13. The IC_{50} for AMP is 1.0µM.

Table 2

Example Compound Number	IC_{50} (human liver FBPase(µM)
12.6	6.5
12.37	4.2
12.35	1.2
13.5	4.7
12.52	2.5
12.54	0.1
12.57	3.8

13.21	2.5
12.61	0.06
13.25	1.8
12.64	0.06
13.52	10.5
13.56	0.78
13.61	0.1
13.66	4.0
12.80	0.035
12.82	0.04
12.79	0.08
15.1	0.18
12.84	0.055
13.96	0.16

Inhibitors of FBPase may also be identified by assaying rat and mouse liver FBPase.

Inhibition of rat liver and mouse liver FBPase

E. coli strain BL21 transformed with a rat liver FBPase-encoding plasmid was obtained from Dr. M. R. El-Maghrabi at the State University of New York at Stony Brook, and purified as described (El-Maghrabi, M.R., and Pilkis, S.J. (1991) Biochem. Biophys. Res. Commun. **176**: 137-144). Mouse liver FBPase was obtained by homogenizing freshly isolated mouse liver in 100 mM Tris-HCl buffer, pH 7.4, containing 1 mM EGTA, and 10% glycerol. The homogenate was clarified by centrifugation, and the 45-75% ammonium sulfate fraction prepared. This fraction was redissolved in the homogenization buffer and desalted on a PD-10 gel filtration column (Biorad) eluted with same. This partially purified fraction was used for enzyme assays. Both rat liver and mouse liver FBPase were assayed as described for human liver FBPase. Generally, as reflected by higher IC_{50} values, the rat and mouse liver enzymes are less sensitive to inhibition by the compounds tested than the human liver enzyme.

The following Table depicts the IC50 values for several compounds prepared in the Examples:

Compound	IC50 Rat Liver (μM)	IC50 Mouse Liver (μM)
12.6	>20	>20
12.37	>20	1.27
12.35	>20	>20
12.52	>20	0.78
12.54	>2	1.07
12.57	>20	>20
12.61	2.18	>20
12.64	0.55	1.07
13.21	>20	>20
13.25	>2	>20
13.56	>2	>20
13.61	>20	>20
13.66	>20	>20
12.80	0.15	0.3
12.82	0.2	0.3
12.79	0.45	0.72
15.1	1.0	1.5
12.84	0.4	0.5
13.96	1.95	0.7

Example B: AMP Site Binding

To determine whether compounds bind to the allosteric AMP binding site of hlFBPase, the enzyme was incubated with radiolabeled AMP in the presence of a range of test compound concentrations. The reaction mixtures consisted of 25 mM ^{3}H-AMP (54 mCi/mmol) and 0 -1000 mM test compound in 25 mM Tris-HCl, pH 7.4, 100 mM KCl and 1 mM $MgCl_2$. 1.45 mg of homogeneous FBPase (±1 nmole) was added last. After a 1 minute incubation, AMP bound to FBPase was separated from unbound AMP by means of a centrifugal ultrafiltration unit ("Ultrafree-MC", Millipore) used according to the instructions of the manufacturer. The radioactivity in aliquots (100 μL) of the upper compartment of the unit (the retentate, which contrains enzyme and label) and the lower compartment (the filtrate, which contains unbound label) were quantified using a Beckman liquid scintillation counter. The amount of AMP bound to the enzyme was estimated by comparing the counts in the filtrate (the unbound label) to the total counts in the retentate.

As evident from Fig. 3, both 5-aminoimidazole-4-carboxamide riboside monophosphate (ZMP) and compound **12.1** displaced AMP from hlFBPase in a dose-dependent manner, indicating that they bind to the same site on the

enzyme as AMP. As expected, compound **12.1** -a more potent hlFBPase inhibitor than ZMP (IC_{50}'s = 2 and 12 μM, respectively)- had a lower ED_{50} for AMP displacement than ZMP (50 vs 250 μM).

Example C: AMP Site/Enzyme Selectivity

To determine the selectivity of compounds towards FBPase, effects of FBPase inhibitors on 5 key AMP binding enzymes were measured using the assays described below:

Adenosine Kinase: Human adenosine kinase was purified from an *E. coli* expression system as described by Spychala *et al.* (Spychala, J., Datta, N.S., Takabayashi, K., Datta, M., Fox, I.H., Gribbin, T., and Mitchell, B.S. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 1232-1237). Activity was measured essentially as described by Yamada *et al.* (Yamada, Y., Goto, H., Ogasawara, N. (1988) *Biochim. Biophys. Acta* **660**, 36-43.) with a few minor modifications. Assay mixtures contained 50 mM TRIS-maleate buffer, pH 7.0, 0.1% BSA, 1 mM ATP 1 mM $MgCl_2$, 1.0 μM [U-^{14}C] adenosine (400-600 mCi/mmol) and varying duplicate concentrations of inhibitor. ^{14}C-AMP was separated from unreacted ^{14}C-adenosine by absorption to anion exchange paper (Whatman) and quantified by scintillation counting.

Adenosine Monophosphate Deaminase: Porcine heart AMPDA was purified essentially as described by Smiley *et al.* (Smiley, K.L., Jr, Berry, A.J., and Suelter, C.H. (1967) *J. Biol. Chem.* **242**, 2502-2506) through the phosphocellulose step. Inhibition of AMPDA activity was determined at 37° C in a 0.1 mL assay mixture containing inhibitor, ~0.005 U AMPDA, 0.1% bovine serum albumin, 10 mM ATP, 250 mM KCl, and 50 mM MOPS at pH 6.5. The concentration of the substrate AMP was varied from 0.125 - 10.0 mM. Catalysis was initiated by the addition of enzyme to the otherwise complete reaction mixture, and terminated after 5 minutes by injection into an HPLC system. Activities were determined from the amount of IMP formed during 5 minutes. IMP was separated from AMP by HPLC using a Beckman Ultrasil-SAX anion exchange column (4.6 mm x 25 cm) with an isocratic buffer system (12.5 mM potassium phosphate, 30 mM KCl, pH 3.5) and detected spectrophotometrically by absorbance at 254 nm.

Phosphofructokinase: Enzyme (rabbit liver) was purchased from Sigma. Activity was measured at 30° C in reactions in which the formation of fructose 1,6-bisphosphate was coupled to the oxidation of NADH via the action of aldolase, triosephosphate isomerase, and α-glycerophosphate dehydrogenase. Reaction mixtures (200 µL) were made up in 96-well microtitre plates and were read at 340 nm in a Molecular Devices Microplate Reader. The mixtures consisted of 200 mM Tris-HCl pH 7.0, 2 mM DTT, 2 mM $MgCl_2$, 0.2 mM NADH, 0.2 mM ATP, 0.5 mM Fructose 6-phosphate, 1 unit aldolase/ml, 3 units/ml triosephosphate isomerase, and 4 units/mL α-glycerophosphate dehydrogenase. Test compound concentrations ranged from 1 to 500 µM. Reactions were started by the addition of 0.0025 units of phosphofructokinase and were monitored for 15 minutes.

Glycogen Phosphorylase: Enzyme (rabbit muscle) was purchased from Sigma. Activity was measured at 37° C in reactions in which the formation of glucose 1-phosphate was coupled to the reduction of NADP via phosphoglucomutase and glucose 6-phosphate dehydrogenase. Assays were performed on 96-well microtitre plates and were read at 340 nm on a Molecular Devices Microplate Reader. Reaction mixtures consisted of 20 mM imidazole, pH 7.4, 20 mM $MgCl_2$, 150 mM potassium acetate, 5 mM potassium phosphate, 1 mM DTT, 1 mg/ml BSA, 0.1 mM NADP, 1 unit/mL phosphoglucomutase, 1 unit/mL glucose 6-phosphate dehydrogenase, 0.5 % glycogen. Test compound concentrations ranged from 1 to 500 µM. Reactions were started by the addition of 17 µg enzyme and were monitored for 20 minutes.

Adenylate Kinase: Enzyme (rabbit muscle) was purchase from Sigma. Activity was measured at 37° C in reaction mixtures (100 µL) containing 100 mM Hepes, pH 7.4, 45 mM $MgCl_2$, 1 mM EGTA, 100 mM KCl, 2 mg/ml BSA, 1 mM AMP and 2 mM ATP. Reactions were started by addition of 4.4 ng enzyme and terminated after 5 minutes by addition of 17 µL perchloric acid. Precipitated protein was removed by centrifugation and the supernatant neutralized by addition of 33 µL 3 M KOH/3 M KH_2CO3. The neutralized solution was clarified by centrifugation and filtration and analyzed for ADP content (enzyme activity) by HPLC using a YMC ODS AQ column (25 X 4.6 cm). A gradient was run from 0.1 M KH2PO4, pH 6, 8 mM tetrabutyl ammonium hydrogen sulfate to 75% acetonitrile. Absorbance was monitored at 254 nM.

Compound **12.1**, a 2 µM hlFBPase inhibitor, was essentially inactive in all of the above described assays except for the AMP deaminase screen: half-maximal inhibition of AMP deaminase was observed at a 42-fold higher concentration than the IC_{50} for FBPase. Compound **12.61** (hlFBPase IC_{50} = 0.055 µM) , in addition to being essentially without effect on adenosine kinase, adenylate kinase, glycogen phosphorylase, and phosphofructokinase, was almost 600-fold less potent on AMP deaminase. Compound **12.64** was tested in the glycogen phosphorylase assay only; no activation of the enzyme was observed at concentrations of drug ranging from 5 to 500 µM. The data suggest that compound **12.61** binds to hlFBPase in a highly selective manner. Table 3 below gives the selectivity data for compounds **12.61** and **12.64**.

Table 3
Selectivity

	Compound **12.1** (µM)	Compound **12.61**	Compound **12.64**
FBPase (inh.)	2.0	0.055	0.055
Adenosine Kinase (inh.)	>>10	>>100	
Adenylate Kinase (inh.)	>>500	>>500	
AMP Deaminase (inh.)	85	32	
Glycogen Phosphorylase (act.)	>>200	>>100	>>500
Phosphofructokinase (act.)	>>200	>>100	

Example D: Inhibition of Gluconeogenesis in Rat Hepatocytes

Hepatocytes were prepared from overnight fasted Sprague-Dawley rats (250-300 g) according to the procedure of Berry and Friend (Berry, M.N., Friend, D.S., 1969, J. Cell. Biol. 43, 506-520) as modified by Groen (Groen, A.K., Sips, H.J., Vervoorn, R.C., Tager, J.M. , 1982, Eur. J. Biochem. 122, 87-93). Hepatocytes (75 mg wet weight/mL) were incubated in 1 ml Krebs-bicarbonate buffer containing 10 mM Lactate, 1 mM pyruvate, 1 mg/mL BSA, and test

compound concentrations from 1 to 500 µM. Incubations were carried out in a 95% oxygen, 5% carbon dioxide atmosphere in closed, 50-mL Falcon tubes submerged in a rapidly shaking water bath (37° C). After 1 hour, an aliquot (0.25 mL) was removed, transferred to an Eppendorf tube and centrifuged. 50 µL of supernatant was then assayed for glucose content using a Sigma Glucose Oxidase kit as per the manufacturer's instructions.

Compounds **12.1**, **12.53**, and **12.61** inhibited glucose production from lactate/pyruvate in isolated rat hepatocytes in a dose-dependent manner, with IC_{50}'s of 110, 2.4 and 3.3 µM, respectively, as shown in Figure 4. IC_{50}'s for other select compounds in this assay are shown in the Table below. Compound **30.2** is a prodrug of compound **12.50.**

Compound	IC50 Glucose Production, µM
12.42	14
12.44	14
12.50	17
12.54	3.6
12.62	5
12.63	16
12.64	2.5
18.2	17
12.80	1.6
12.82	2.2
12.79	1.0
12.84	9
15.1	16

FBPase from rat liver is less sensitive to AMP than that from human liver. IC_{50} values are consequently higher in rat hepatocytes than would be expected in human hepatocytes.

Example E: Blood Glucose Lowering in Fasted Rats

Sprague Dawley rats (250-300 g) were fasted for 18 hours and then dosed intraperitoneally with 20 mg/kg of compounds **12.53**, **12.61**, or **12.64**. The vehicle used for drug administration was 50 mM sodium bicarbonate. Blood samples were obtained from the tail vein of conscious animals just prior to

injection and one hour post injection. Blood glucose was measured using a HemoCue Inc. glucose analyzer according to the instructions of the manufacturer.

Compound **12.53** lowered blood glucose by 55±14%, compound **12.61** by 48±15%, and compound **12.64** by 64.6±24%.

Example F: Effect of Compound 12.64 on gluconeogenesis from lactate/pyruvate in rat hepatocytes: glucose production inhibition and fructose 1,6-bisphosphate accumulation

Isolated rat hepatocytes were prepared as described in Example D and incubated under the identical conditions described. Reactions were terminated by removing an aliquot (250 µL) of cell suspension and spinning it through a layer of oil (0.8 mL silicone/mineral oil, 4/1) into a 10% perchloric acid layer (100 µL). After removal of the oil layer, the acidic cell extract layer was neutralized by addition of 1/3rd volume of 3 M KOH/3 M KH2CO3. After thorough mixing and centrifugation, the supernatant was analyzed for glucose content as described in Example D, and also for fructose 1,6-bisphosphate. Fructose 1,6-bisphosphate was assayed spectrophotometrically by coupling its enzymatic conversion to glycerol 3-phosphate to the oxidation of NADH, which was monitored at 340 nm. Reaction mixtures (1 mL consisted of 200 mM Tris-HCl, pH 7.4, 0.3 mM NADH, 2 units/mL glycerol 3-phsophate dehydrogenase, 2 units/ml triosephosphate isomerase, and 50-100 µL cell extract. After a 30 minute preincubation at 37°C, 1 unit/mL of aldolase was added and the change in absorbance measured until a stable value was obtained. 2 moles of NADH are oxidized in this reaction per mole of fructose 1,6-bisphosphate present in the cell extract.

As shown in Figure 5, compound **12.64** inhibited glucose production from lactate/pyruvate in rat hepatocytes (IC50 approx. 3 µM) The dose-dependent accumulation of fructose 1,6 bisphosphate (the substrate of FBPase) that occurred upon cell exposure to compound **12.64** is consistent with the inhibition of FBPase.

Example G: Analysis of Drug Levels And Liver Accumulation in Rats

Sprague-Dawley rats (250-300 g) were fasted for 18 hours and then dosed intraperitoneally either with saline (n = 3) or 20 mgs/kg of FBPase

inhibitor (n = 4). The vehicle used for drug administration was 10 mM bicarbonate. One hour post injection rats were anesthetized with halothane and a liver biopsy (approx. 1 g) was taken as well as a blood sample (2 ml) from the posterior vena cava. A heparin flushed syringe and needle was used for blood collection. The liver sample was immediately homogenized in ice-cold 10% perchloric acid (3 mL), centrifuged, and the supernatant neutralized with 1/3rd volume of 3 M KOH/3 M KH_2CO3. Following centrifugation and filtration, 50 μl of the neutralized extract was analyzed for FBPase inhibitor content by HPLC. A reverse phase YMC ODS AQ column (250 x 4.6 cm) was used and eluted with a gradient from 10 mM sodium phosphate pH 5.5 to 75% acetonitrile. Absorbance was monitored at 310 nm. (The concentration of fructose-1,6-bisphosphate in liver is also quantified using the method described in Example F. An elevation of fructose-1,6-bisphosphate levels in the livers from the drug-treated group is consistent with the inhibition of glucose production at the level of FBPase in the gluconeogenic pathway.) Blood glucose was measured in the blood sample as described in Example D. Plasma was then quickly prepared by centrifugation and extracted by addition of methanol to 60% (v/v). The methanolic extract was clarified by centrifugation and filtration and then analyzed by HPLC as described above.

Compound **12.64** achieved plasma acid liver levels of 85 μM and 90 nmoles/gram, respectively, one hour post injection of a 20 mg/kg dose.

Example H: Blood Glucose Lowering in Zucker Diabetic Fatty Rats

Zucker Diabetic Fatty rats purchased at 7 weeks of age are used at age 16 weeks in the 24-hour fasted state. The rats are purchased from Genetics Models Inc. and fed the recommended Purina 5008 diet (6.5% fat). Their fasting hyperglycemia at 24 hours generally ranges from 150 mg/dL to 310 mg/dL blood glucose.

FBPase inhibitor is administered at a dose of 50 mg/kg by intraperitoneal injection (n = 6). The stock solution is made up at 25 mg/mL in deionized water and adjusted to neutratility by dropwise addition of 5 N NaOH. 5 control animals are dosed with saline. Blood glucose is measured at the time of dosing and 2 hours post dose as described in Example D.

Example I: Inhibition of gluconeogenesis by FBPase inhibitor in Zucker Diabetic Fatty rats

Nine Zucker Diabetic Fatty rats (16-weeks old, Genetics Models Inc., Indianapolis, Indiana) were fasted at midnight and instrumented with jugular catheters the following morning. At noon, a dose of 50 mg/kg compound **12.64** (n = 3) or saline (n = 3) was administered as a bolus via the jugular catheter. After 50 minutes a bolus of ^{14}C-sodium bicarbonate (40 µCi/100 g body weight) was administered via the same route. 20 minutes later, the animals were quickly anesthetized with intravenous pentobarbitol and a blood sample (1.5 mL) was taken by cardiac puncture. Blood (0.5 mL) was diluted into 6 mL deionized water and protein precipitated by addition of 1 mL zinc sulfate (0.3 N) and 1 mL barium hydroxide (0.3 N). The mixture was centrifuged (20 minutes, 1000 x g) and 5 mL of the resulting supernatant was then combined with 1 g of a mixed bed ion exchange resin (1 part AG 50W-X8, 100-200 mesh, hydrogen form and 2 parts of AG 1-X8, 100-200 mesh, acetate form) to separate ^{14}C-bicarbonate from ^{14}C-glucose. The slurry was shaken at room temperature for four hours and then allowed to settle. An aliquot of the supernatant (0.5 mL) was then counted in 5 mL scintillation cocktail.

As indicated in the table below, compound **12.64** reduced the incorporation of ^{14}C-bicarbonate into ^{14}-C-glucose by approximately 50%.

Treatment	^{14}C-Glucose Produced (cpm/mL blood)	% Glucose Produced
Saline (n = 3)	66,651 ± 2365	100
12.64 (n = 3)	32,827 ± 6130	49.2

Example J: Blood Glucose Lowering in the Streptozotocin-treated Rat

Diabetes was induced in male Sprague-Dawley rats (250-300 g) by intraperitoneal injection of 55 mg/kg streptozotocin (Sigma Chemical Co.). Six days later, 24 animals were selected with fed blood glucose values (8 am) between 350 and 600 mg/dL and divided into two statistically equivalent groups. Blood glucose was measured in blood obtained from a tail vein nick by means of a HemoCue Inc. (Mission Viejo, CA) glucose analyzer. One group of 12 subsequently received compound **12.64** (100 mg/kg intraperitoneally) and

the other 12 ("controls") an equivalent volume of saline. Food was removed from the animals. Blood glucose was measured in each animal four hours after dosing, and a second dose of drug or saline was then administered. Four hours later, a final blood glucose measurement was made. As shown in the table below, compound **12.64** significantly reduced fasting blood glucose levels in the treated animal group, 8 hours after the initial dose:

Treatment	Blood glucose, mg/dl T=0h	T=8h	p value (relative to controls)
Saline (n = 12)	489 ± 20	404 ± 19	
12.64 (n = 12)	488 ± 16	271 ± 29	0.001

Example K: Glucose lowering following oral administration of the Compound of Example 12.64

Compound **12.64** was administered by oral gavage at doses of 30, 100 and 250 mg/kg to 18-hour fasted, Sprague Dawley rats (250-300g; n= 4 - 5/group). The compound was prepared in deionized water, adjusted to neutrality with sodium hydroxide, and brought into solution by sonication prior to administration. Blood glucose was measured immediately prior to dosing, and at 1 hour intervals thereafter. Blood samples were obtained from the tail vein, and measurments made by means of a Hemocue glucose analyzer (Hemocue Inc, Mission Viejo, California) used according to the manufacturer's instructions. The 30 and 100 mg/kg doses were without effect, but profound hypoglycemia was elicited by the 250 mg/kg dose in 4 out of 5 animals dosed, within 1 hour of administration. The average glucose lowering in the four responding animals was 62 ± 8.6 % relative to saline-treated controls at the 1 hour time point.

Example L: Estimation of the oral bioavailability of prodrugs of phosphonic acids:

Prodrugs were dissolved in 10% ethanol/90% polyethylene glycol (mw 400) and administered by oral gavage at doses of approximately 20 or 40 mg/kg parent compound equivalents to 6-hour fasted, Sprague Dawley rats (220-240 g). The rats were subsequently placed in metabolic cages and urine was collected for 24 hours. The quantity of parent compound excreted into urine was determined by HPLC analysis. An ODS column eluted with a gradient from potassium phosphate buffer, pH 5.5 to acetonitrile was employed

for these measurements. Detection was at 310-325 nm. The percentage oral bioavailability was estimated by comparison of the recovery in urine of the parent compound generated from the prodrug, to that recovered in urine 24 hours after intravenous administration of unsubstituted parent compound at approximately 10 mg/kg. Parent compounds were typically dissolved in dimethyl sulfoxide, and administered via the tail vein in animals that were briefly anesthetized with halothane.

For Compound A, 6-amino-9-neopentyl, 8-(2-(5-diisobutyryloxymethylphosphono)furanyl purine, a prodrug of parent Compound B, 6-amino-9-neopentyl-8-(2-(5-phosphono)furanyl purine, 6.2% of an oral dose of approximately 20 mg/kg was recovered in urine. For the parent compound, 76.8% of an intravenous dose of approximately 10 mg/kg was recovered. The oral bioavailability of this prodrug was therefore calculated to be 6.2/76.8, or approximately 8%. The oral bioavailability of select other prodrugs are shown in the table below:

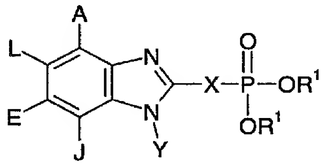
Prodrug (Example No.)	Parent compound (Example No.)	%Oral bioavailability
31.14	13.17	12.5
18.7	15.1	6.9
Compound C*	Compound B**	5.3
31.13	13.17	10.9
31.15	13.17	14.1

* Compound C is 6-amino-9-neopentyl-8-(2-(5-dipivaloyloxymethyl-phosphono)furanyl purine.

** Compound B is 6-amino-9-neopentyl-8-[2-(5-phosphono)]furanyl purine.

We claim:

1. The compounds of formula (I):



I

wherein:

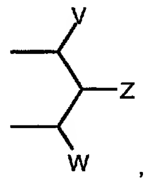
A, E, and L are selected from the group consisting of $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2{}_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R^{10};

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, -NH_2, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, -NH_2 and -OR^3; and

pharmaceutically acceptable prodrugs and salts thereof; with the provisos that:

a) R^1 is not lower alkyl of 1-4 carbon atoms;

b) when X is alkyl or alkene, then A is -N($R^8{}_2$);

c) X is not alkylamine and alkylaminoalkyl substituted with phosphonic esters and acids; and

d) A, L, E, J, Y, and X together may only form 0-2 cyclic groups.

2. The compounds of claim 1 wherein when X is substituted with a phosphonic acid or ester, then A is -N($R^8{}_2$) and Y is not -H.

3. The compounds of claim 1 wherein X is not substituted with a phosphonic acid or ester.

4. The compounds of claim 1, with the additional proviso that when X is aryl or alkylaryl, said aryl or alkylaryl group is not linked 1,4 through a six-membered aromatic ring.

5. The compounds of claim 1 wherein A, L, and E are independently selected from the group consisting of -H, $-NR^8_2$, $-NO_2$, hydroxy, halogen, $-OR^7$, alkylaminocarbonyl, $-SR^7$, lower perhaloalkyl, and C1-C5 alkyl, or together E and J together form a cyclic group.

6. The compound of claim 5 wherein A, L and E are independently selected from the group consisting of $-NR^8_2$, -H, hydroxy, halogen, lower alkoxy, lower perhaloalkyl, and lower alkyl.

7. The compounds of claim 1 wherein A is selected from the group consisting of $-NR^8_2$, -H, halogen, lower perhaloalkyl, and lower alkyl.

8. The compounds of claim 1 wherein L and E are independently selected from the group consisting of -H, lower alkoxy, lower alkyl, and halogen.

9. The compounds of claim 1 wherein J is selected from the group consisting of -H, halogen, lower alkyl, lower hydroxyalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower perhaloalkyl, lower alkenyl, lower alkynyl, lower aryl, heterocyclic, and alicyclic, or together with Y forms a cyclic group.

10. The compounds of claim 9 wherein J is selected from the group consisting of -H, halogen, lower alkyl, lower hydroxyalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower alkenyl, alicyclic, and aryl.

11. The compounds of claim 1 wherein Y is selected from the group consisting of -H, aralkyl, aryl, alicyclic, and alkyl, all except -H may be optionally substituted.

12. The compounds of claim 11 wherein Y is selected from the group consisting of alicyclic and lower alkyl.

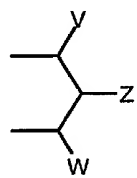
13. The compounds of claim 1 wherein X is selected from the group consisting of alkyl, alkynyl, alkoxyalkyl, alkylthio, aryl, alkylaminocarbonyl, alkylcarbonylamino, 1,1-dihaloalkyl, carbonylalkyl, alkyl(OH), and alkyl(sulfonate).

14. The compounds of claim 13 wherein X is selected from the group consisting of heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, alkyl(sulfonate), and alkoxyalkyl.

15. The compounds of claim 14 wherein X is selected from the group consisting of heteroaryl, alkylaminocarbonyl, and alkoxyalkyl.

16. The compounds of claim 15 wherein X is selected from the group consisting of methylaminocarbonyl, methoxymethyl and furanyl.

17. The compounds of claim 1 wherein each R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted phenyl, optionally substituted benzyl, optionally substituted alkylaryl, $-C(R^2)_2OC(O)R^3$, $C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2$-OC(O)SR^3, -alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxyl, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are alkyl-S-S-alkyl to form a cyclic group, or R^1 and R^1 together are



,

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R^9; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy,

alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

18. The compounds of claim 17 wherein each R^1 is independently selected from the group consisting of optionally substituted phenyl, optionally substituted benzyl, $-C(R^2)_2OC(O)R^3$, and -H.

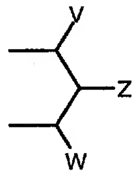
19. The compounds of claim 18 wherein R^1 is H.

20. The compounds of claim 17 wherein at least one R^1 is aryl, or $-C(R^2)_2$-aryl.

21. The compounds of claim 17 wherein at least one R^1 is $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-OC(O)OR^3$, $-C(R^2)_2-OC(O)SR^3$.

22. The compounds of claim 17 wherein at least one R^1 is alkyl-S-S-alkylhydroxyl, -alkyl-S-C(O)R^3, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are alkyl-S-S-alkyl to form a cyclic group.

23. The compounds of claim 1 wherein together R^1 and R^1 are



wherein:

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

24. The compounds of claim 23 wherein V and W both form a 6-membered carbocyclic ring substituted with 0-4 groups, selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, and alkoxy; and Z is $-R^2$.

25. The method of claim 23 wherein V and W are hydrogen; and Z is selected from the group consisting of hydroxyalkyl, acyloxyalkyl, alkyloxyalkyl, and alkoxycarboxyalkyl.

26. The method of claim 23 wherein V and W are independently selected from the group consisting of hydrogen, optionally substituted aryl, and optionally substituted heteroaryl, with the proviso that at least one of V and W is optionally substituted aryl or optionally substituted heteroaryl.

27. The compounds of claim 1 wherein together R^1 and R^1 are optionally substituted lactones attached at the omega position.

28. The compounds of claim 17 wherein R^1 is alicyclic where the cyclic moiety contains carbonate or thiocarbonate.

29. The compounds of claim 28 wherein together R^1 and R^1 are optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen.

30. The compounds of claim 1 wherein

A, L and E are independently selected from the group consisting of $-NR^8_2$, -H, hydroxy, halogen, lower alkoxy, lower alkyl, and lower perhaloalkyl;

X is selected from the group consisting of aryl, alkoxyalkyl, alkyl, alkylthio, 1,1-dihaloalkyl, carbonylalkyl, alkyl(hydroxy), alkyl(sulfonate), alkylaminocarbonyl, and alkylcarbonylamino;

and each R^4 and R^7 is independently selected from the group consisting of -H and lower alkyl.

31. The compounds of claim 30 wherein A, L, and E are independently selected from the group consisting of -H, lower alkyl, halogen, and $-NR^8_2$;

J is selected from the group consisting of -H, halogen, haloalkyl, hydroxyalkyl, $-R^8_2$ N-alkyl, lower alkyl, lower aryl, heterocyclic and alicyclic, or together with Y forms a cyclic group; and

X is selected from the group consisting of heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, and alkoxyalkyl.

32. The compounds of claim 31 wherein A is selected from the group consisting of -H, $-NH_2$, -F, and $-CH_3$;

L is selected from the group consisting of -H, -F, $-OCH_3$, Cl and $-CH_3$;

E is selected from the group consisting of -H, and -Cl;

J is selected from the group consisting of -H, halo, C1-C5 hydroxyalkyl, C1-C5 haloalkyl, C1-C5 $R^8{}_2$ N-alkyl, C1-C5 alicyclic, and C1-C5 alkyl;

X is $-CH_2OCH_2-$, 2,5-furanyl; and

Y is lower alkyl.

33. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -H, Y is isobutyl, and X is 2,5-furanyl.

34. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -Cl, Y is isobutyl, and X is 2,5-furanyl.

35. The compounds of claim 32 where A is -H, L is -H, E is -Cl, J is -H, Y is isobutyl, and X is 2,5-furanyl.

36. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -H, Y is cyclopropylmethyl, and X is 2,5-furanyl.

37. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is ethyl, Y is isobutyl, and X is 2,5-furanyl.

38. The compounds of claim 32 where A is $-CH_3$, L is -Cl, E is -H, J is -H, Y is isobutyl, and X is 2,5-furanyl.

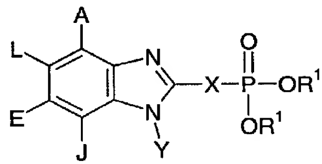
39. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -Br, Y is isobutyl, and X is $-CH_2OCH_2$.

40. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is selected from the group consisting of bromopropyl, bromobutyl, chlorobutyl, cyclopropyl, hydroxypropyl, N,N-dimethylaminopropyl, and X is 2,5-furanyl.

41. The compound of claim 32 wherein A is $-CH_3$, L is $-CH_3$, E is $-CH_3$, J is $-CH_3$, Y is cyclopropylmethyl, and X is 2,5-furanyl.

42. The compounds of claims 33, 34, 35, 36, 37, 38, 39, 40, or 41 wherein R^1 is pivaloyloxymethyl or their HCl salts.

43. A method of treating an animal for diabetes mellitus, comprising administering to said animal a therapeutically effective amount of a compound of formula 1:



wherein:

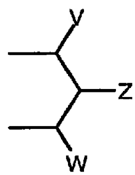
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

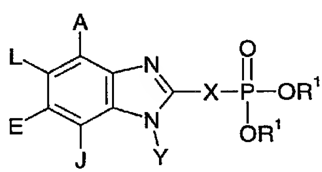
R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

44. A method of lowering blood glucose levels in an animal in need thereof, comprising administering to said animal a pharmaceutically acceptable amount of a compound of formula 1:



wherein:

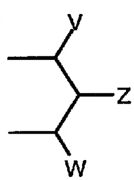
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R^9; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

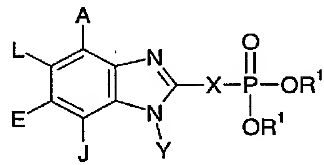
R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

45. A method of inhibiting FBPase at the AMP site in patients in need thereof, comprising administering to said patients an FBPase inhibitory amount of a compound of formula 1:



wherein:

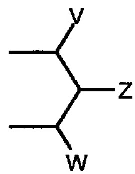
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

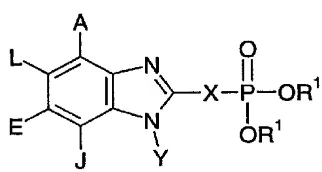
R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

46. A method of inhibiting gluconeogenesis in animal in need thereof, comprising administering to said animal an effective amount of a compound of formula 1:



wherein:

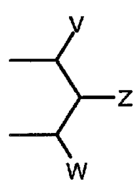
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

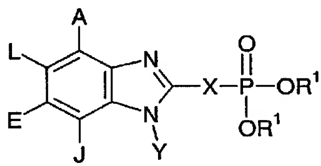
R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

47. A method of treating an animal for a disease derived from abnormally elevated insulin levels, comprising administering to said animal a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor which binds to the AMP site of FBPase.

48. The method of claim 47 wherein said inhibitor is a compound of formula 1:



wherein:

A, E, and L are selected from the group consisting of $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

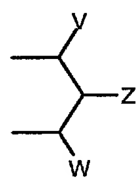
J is selected from the group consisting of $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl,

alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



,

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

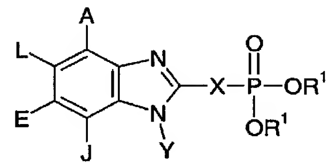
R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

49. The method of claim 47 wherein said disease is atherosclerosis.

50. A method of treating an animal with excess glycogen storage disease, comprising administering to said animal in need thereof a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor which binds to the AMP site of FBPase.

51. The method of claim 50 wherein said inhibitor is a compound of formula 1:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

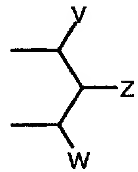
J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$,

$-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

52. The methods of claims 43, 44, 45, 46, 47, 48, 49, 50, or 51 wherein said compounds are administered orally.

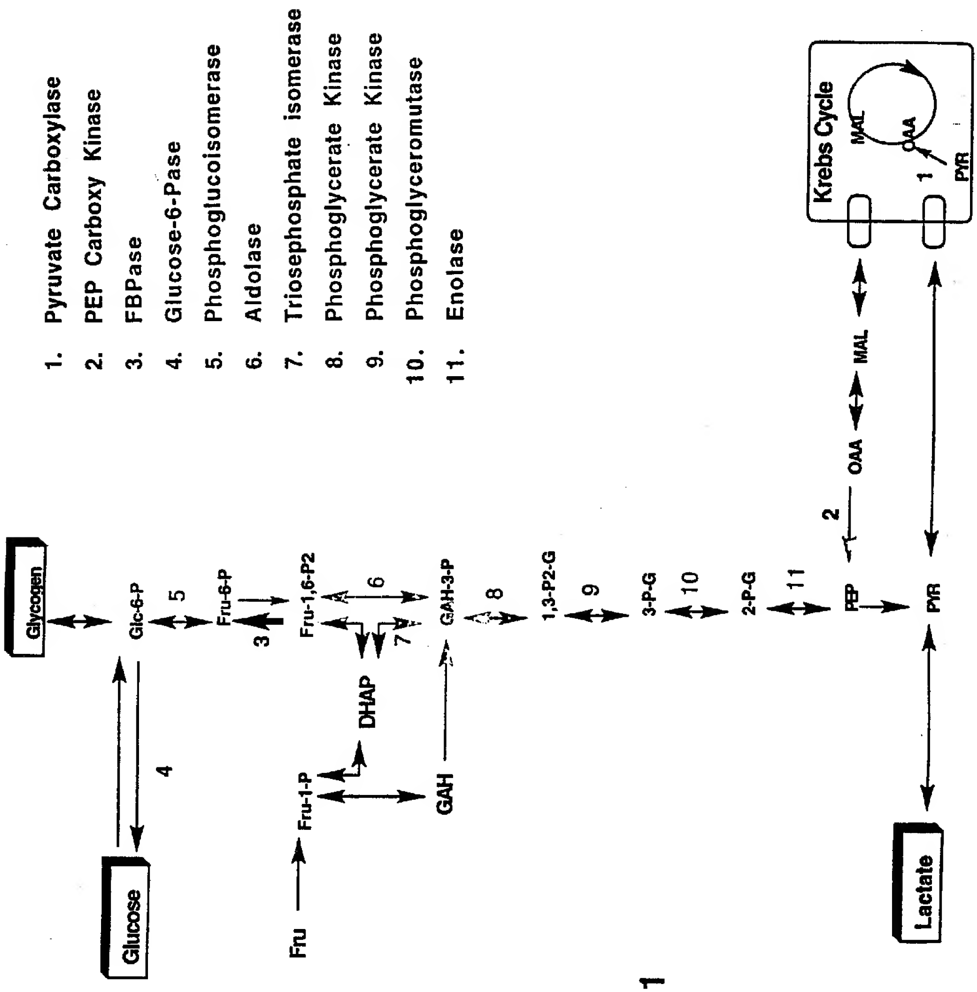

1. Pyruvate Carboxylase
2. PEP Carboxy Kinase
3. FBPase
4. Glucose-6-Pase
5. Phosphoglucoisomerase
6. Aldolase
7. Triosephosphate isomerase
8. Phosphoglycerate Kinase
9. Phosphoglycerate Kinase
10. Phosphoglyceromutase
11. Enolase
Glycogen
Glc-6-P
Fru-6-P
Fru-1,6-P2
GAH-3-P
1,3-P2-G
3-P-G
2-P-G
PEP
PYR
Glucose
Fru
Fru-1-P
DHAP
GAH
OAA
MAL
Krebs Cycle
Lactate

FIGURE 1

In Vitro Inhibition of hlFBPase

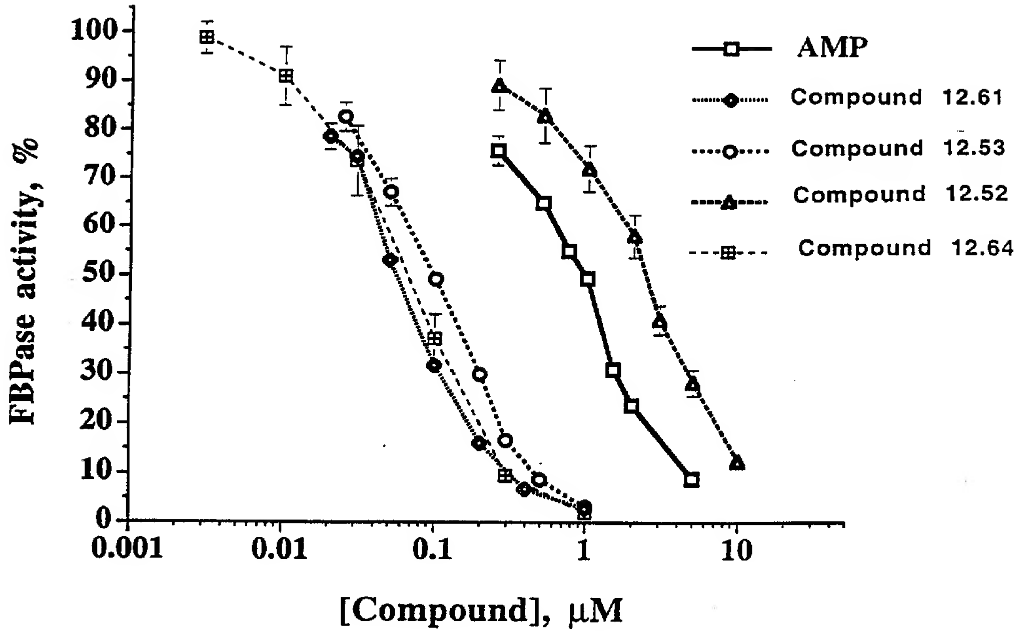


FIGURE 2

Displacement of AMP from hlFBPase

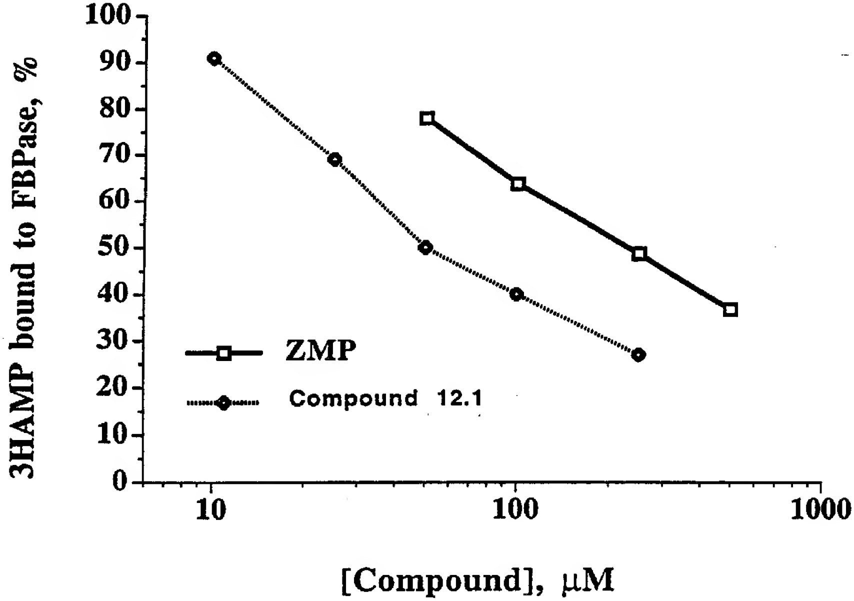


FIGURE 3

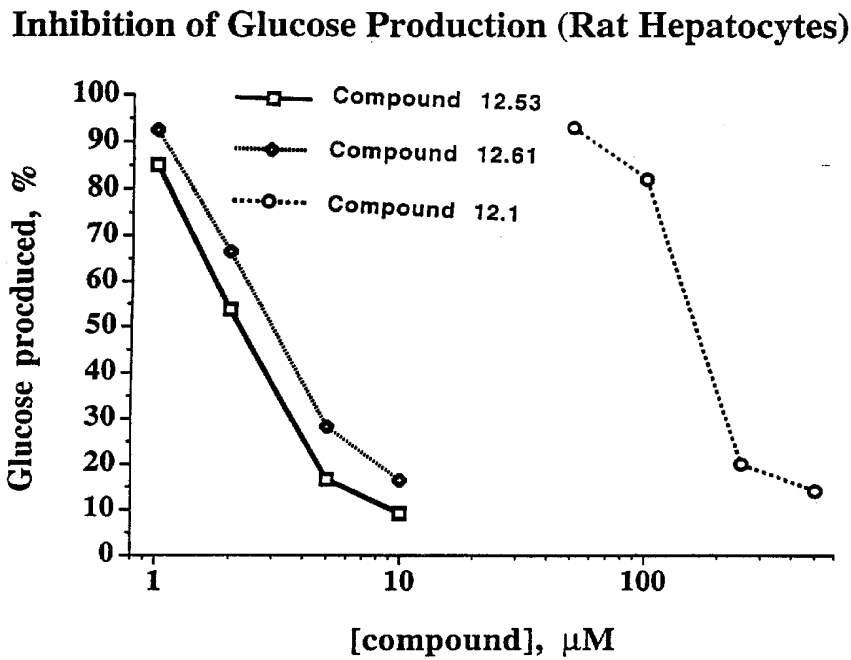

Inhibition of Glucose Production (Rat Hepatocytes)
Compound 12.53
Compound 12.61
Compound 12.1
Glucose procduced, %
100
90
80
70
60
50
40
30
20
10
0
1
10
100
[compound], μM

FIGURE 4

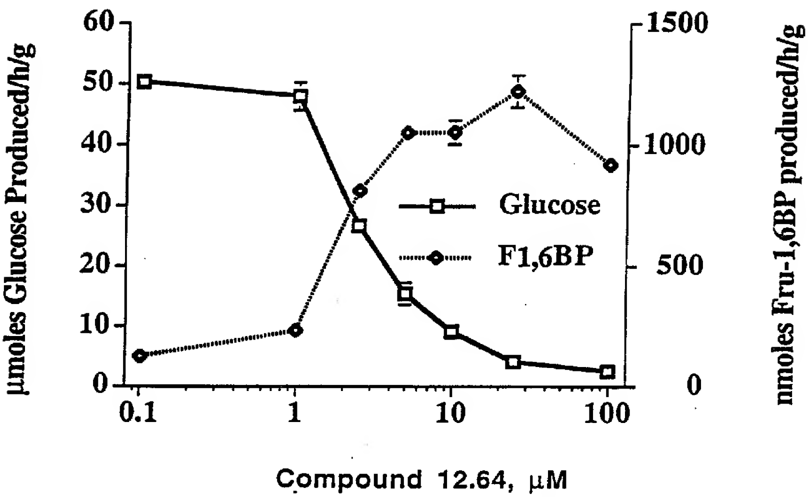

60
50
40
30
20
10
0
1500
1000
500
0
µmoles Glucose Produced/h/g
nmoles Fru-1,6BP produced/h/g
Glucose
F1,6BP
0.1
1
10
100
Compound 12.64, µM

FIGURE 5

INTERNATIONAL SEARCH REPORT

International Application No
PC\ . S 98/04498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07F9/6506 A61K31/675 C07F9/6558

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 427 799 B (GENSIA PHARMACEUTICALS, INC.) 30 November 1994 cited in the application see the whole document ---	1-52
Y	EP 0 354 322 A (AMERICAN CYANAMID CO.) 14 February 1990 see the whole document ---	1-52
Y	WO 94 07867 A (PFIZER INC.) 14 April 1994 see the whole document --- -/--	1-52

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1998	26 jun 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOHICHIRO YOSHINO: "Organic phosphorus compounds.2. Synthesis and coronary vasodilatator activity of (Benzothiazolylbenzyl)phosphonate derivatives." JOURNAL OF MEDICINAL CHEMISTRY., vol. 32, no. 7, - July 1989 WASHINGTON US, pages 1528-1532, XP002066780 cited in the application see the whole document	1-52
Y	EP 0 620 227 A (HOECHST JAPAN LTD.) 19 October 1994 cited in the application see the whole document	1-52
Y	WO 94 20508 A (EISAI CO. LTD.) 15 September 1994 see page 242, examples 305 and 306; claims	1-52
Y	EP 0 604 657 A (OTSUKA PHARMACEUTICAL FACTORY, INC.) 6 July 1994 see page 4, lines 8-14; page 11, table 1; page 16, examples 24-26	1-52
Y	US 5 021 443 A (NICOLE BRU-MAGNIEZ) 4 June 1991 see column 9 and claims	1-52
A	EP 0 012 909 A (BAYER AG) 9 July 1980 cited in the application see claim 1	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/04498

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 43 - 52
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

mation on patent family members

International Application No
PC1, .S 98/04498

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 427799	B	22-05-1991	US	5082829	A	21-01-1992
			US	5200525	A	06-04-1993
			DE	69014562	D	12-01-1995
			DE	69014562	T	22-06-1995
			EP	0427799	A	22-05-1991
			AT	114474	T	15-12-1994
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			AU	5236093	A	24-02-1994
			CA	2008325	A	24-07-1990
			DK	427799	T	08-05-1995
			IE	75372	B	10-09-1997
			JP	3504728	T	17-10-1991
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EP 354322	A	14-02-1990	US	4943629	A	24-07-1990
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			JP	7507072	T	03-08-1995
			NO	951155	A	26-05-1995
			NZ	254550	A	22-08-1997
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EP 620227	A	19-10-1994	JP	6298779	A	25-10-1994
			AU	673895	B	28-11-1996
			AU	5943294	A	20-10-1994
			CA	2121313	A	16-10-1994
			FI	941712	A	16-10-1994
			HU	68774	A	28-07-1995
			NO	941336	A	17-10-1994
			US	5441945	A	15-08-1995
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		ZA 9401575 A	13-10-1994
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		AU 7087491 A	22-08-1991
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		DK 442820 T	05-02-1996
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		AT 3772 T	15-06-1983
		JP 55087796 A	02-07-1980
		US 4278791 A	14-07-1981

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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(11) International Publication Number: WO 98/39343

(43) International Publication Date: 11 September 1998 (11.09.98)

(21) International Application Number: PCT/US98/04498

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(30) Priority Data: 60/040,627 7 March 1997 (07.03.97) US

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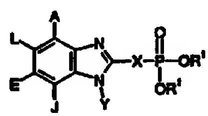
(54) Title: NOVEL BENZIMIDAZOLE INHIBITORS OF FRUCTOSE–1,6–BISPHOSPHATASE

(57) Abstract



(1)

Novel benzimidazole compounds of structure (1) and their use as fructose–1,6–bisphosphatase inhibitors is described wherein A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, –CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloakolxy, C1–C5 alkyl, C2–C5 alkenyl, C2–C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic; J is selected from the group consisting $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, –CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl; X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1–dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic; Y is selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic; and pharmaceutically acceptable prodrugs and salts thereof.

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NOVEL BENZIMIDAZOLE INHIBITORS OF FRUCTOSE 1,6-BISPHOSPHATASE

Field of the Invention

This invention relates to novel benzimidazole compounds that are inhibitors of Fructose-1,6-bisphosphatase at the AMP site. The invention also relates to the preparation and use of these benzimidazole analogs in the treatment of diabetes, and other diseases where the inhibition of gluconeogenesis, control of blood glucose levels, reduction in glycogen stores, or reduction in insulin levels is beneficial.

Background and Introduction to the Invention

Diabetes mellitus (or diabetes) is one of the most prevalent diseases in the world today. Diabetes patients have been divided into two classes, namely type I or insulin-dependent diabetes mellitus and type II or non-insulin dependent diabetes mellitus (NIDDM). Non-insulin-dependent diabetes mellitus (NIDDM) accounts for approximately 90% of all diabetics and is estimated to affect 12-14 million adults in the U. S. alone (6.6% of the population). NIDDM is characterized by both fasting hyperglycemia and exaggerated postprandial increases in plasma glucose levels. NIDDM is associated with a variety of long-term complications, including microvascular diseases such as retinopathy, nephropathy and neuropathy, and macrovascular diseases such as coronary heart disease. Numerous studies in animal models demonstrate a causal relationship between long term complications and hyperglycemia. Recent results from the Diabetes Control and Complications Trial (DCCT) and the Stockholm Prospective Study demonstrate this relationship for the first time in man by showing that insulin-dependent diabetics with tighter glycemic control are at substantially lower risk for development and progression of these complications. Tighter control is also expected to benefit NIDDM patients.

Current therapies used to treat NIDDM patients entail both controlling lifestyle risk factors and pharmaceutical intervention. First-line therapy for NIDDM is typically a tightly-controlled regimen of diet and exercise since an overwhelming number of NIDDM patients are overweight or obese (≈ 67%) and since weight loss can improve insulin secretion, insulin sensitivity and lead to normoglycemia. Normalization of blood glucose occurs in less than 30% of these patients due to poor compliance and poor response. Patients with

hyperglycemia not controlled by diet alone are subsequently treated with oral hypoglycemics or insulin. Until recently, the sulfonylureas were the only class of oral hypoglycemic agents available for NIDDM. Treatment with sulfonylureas leads to effective blood glucose lowering in only 70% of patients and only 40% after 10 years of therapy. Patients that fail to respond to diet and sulfonylureas are subsequently treated with daily insulin injections to gain adequate glycemic control.

Although the sulfonylureas represent a major therapy for NIDDM patients, four factors limit their overall success. First, as mentioned above, a large segment of the NIDDM population do not respond adequately to sulfonylurea therapy (*i.e.* primary failures) or become resistant (*i.e.* secondary failures). This is particularly true in NIDDM patients with advanced NIDDM since these patients have severely impaired insulin secretion. Second, sulfonylurea therapy is associated with an increased risk of severe hypoglycemic episodes. Third, chronic hyperinsulinemia has been associated with increased cardiovascular disease although this relationship is considered controversial and unproven. Last, sulfonylureas are associated with weight gain, which leads to worsening of peripheral insulin sensitivity and thereby can accelerate the progression of the disease.

Recent results from the U.K. Diabetes prospective study also showed that patients undergoing maximal therapy of a sulfonylurea, metformin, or a combination of the two, were unable to maintain normal fasting glycemia over the six year period of the study. U.K. Prospective Diabetes Study 16. Diabetes, 44:1249-158 (1995). These results further illustrate the great need for alternative therapies. Three therapeutic strategies that could provide additional health benefits to NIDDM patients beyond the currently available therapies, include drugs that would: (i) prevent the onset of NIDDM; (ii) prevent diabetic complications by blocking detrimental events precipitated by chronic hyperglycemia; or (iii) normalize glucose levels or at least decrease glucose levels below the threshold reported for microvascular and macrovascular diseases.

Hyperglycemia in NIDDM is associated with two biochemical abnormalities, namely insulin resistance and impaired insulin secretion. The relative roles of these metabolic abnormalities in the pathogenesis of NIDDM has been the subject of numerous studies over the past several decades. Studies of offspring and siblings of NIDDM patients, mono- and dizygotic twins,

and ethnic populations with high incidence of NIDDM (*e.g.* Pima Indians) strongly support the inheritable nature of the disease.

Despite the presence of insulin resistance and impaired insulin secretion, fasting blood glucose (FBG) levels remain normal in pre-diabetic patients due to a state of compensatory hyperinsulinemia. Eventually, however, insulin secretion is inadequate and fasting hyperglycemia ensues. With time insulin levels decline. Progression of the disease is characterized by increasing FBG levels and declining insulin levels.

Numerous clinical studies have attempted to define the primary defect that accounts for the progressive increase in FBG. Results from these studies indicate that excessive hepatic glucose output (HGO) is the primary reason for the elevation in FBG with a significant correlation found for HGO and FBG once FBG exceeds 140 mg/dL. Kolterman, et al., J. Clin. Invest. 68:957, (1981); DeFronzo Diabetes 37:667 (1988).

HGO comprises glucose derived from breakdown of hepatic glycogen (glycogenolysis) and glucose synthesized from 3-carbon precursors (gluconeogenesis). A number of radioisotope studies and several studies using ^{13}C-NMR spectroscopy have shown that gluconeogenesis contributes between 50-100% of the glucose produced by the liver in the postabsorptive state and that gluconeogenesis flux is excessive (2- to 3-fold) in NIDDM patients. Magnusson, et al. J. Clin. Invest. 90:1323-1327 (1992); Rothman, et al., Science 254: 573-76 (1991); Consoli, et a l. Diabetes 38:550-557 (1989).

Gluconeogenesis from pyruvate is a highly regulated biosynthetic pathway requiring eleven enzymes (Figure 1). Seven enzymes catalyze reversible reactions and are common to both gluconeogenesis and glycolysis. Four enzymes catalyze reactions unique to gluconeogenesis, namely pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase. Overall flux through the pathway is controlled by the specific activities of these enzymes, the enzymes that catalyzed the corresponding steps in the glycolytic direction, and by substrate availability. Dietary factors (glucose, fat) and hormones (insulin, glucagon, glucocorticoids, epinephrine) coordinatively regulate enzyme activities in the gluconeogenesis and glycolysis pathways through gene expression and post-translational mechanisms.

Of the four enzymes specific to gluconeogenesis, fructose-1,6-bisphosphatase (hereinafter "FBPase") is the most suitable target for a gluconeogenesis inhibitor based on efficacy and safety considerations. Studies indicate that nature uses the FBPase/PFK cycle as a major control point (metabolic switch) responsible for determining whether metabolic flux proceeds in the direction of glycolysis or gluconeogenesis. Claus, et al., Mechanisms of Insulin Action, Belfrage, P. editor, pp.305-321, Elsevier Science 1992; Regen, et al. J. Theor. Biol., 111:635-658 (1984); Pilkis, et al. Annu. Rev. Biochem, 57:755-783 (1988). FBPase is inhibited by fructose-2,6-bisphosphate in the cell. Fructose-2,6-bisphosphate binds to the substrate site of the enzyme. AMP binds to an allosteric site on the enzyme.

Synthetic inhibitors of FBPase have also been reported. McNiel reported that fructose-2,6-bisphosphate analogs inhibit FBPase by binding to the substrate site. J. Med. Chem., 106:7851 (1984); U.S. Patent No. 4,968,790 (1984). These compounds, however, were relatively weak and did not inhibit glucose production in hepatocytes presumably due to poor cell penetration.

Gruber reported that some nucleosides can lower blood glucose in the whole animal through inhibition of FBPase. These compounds exert their activity by first undergoing phosphorylation to the corresponding monophosphate. EP 0 427 799 B1.

Gruber et al. U.S. Patent No. 5,658,889 described the use of inhibitors of the AMP site of FBPase to treat diabetes.

J. Med. Chem. 32:1528-32 (1989) discloses lower alkyl phosphonic esters of benzimidazole compounds where X in formula 1 of the present invention is -pyridyl-CH_2-. This publication discusses Ca^{2+} antagonist activity. There is no suggestion that the disclosed compounds were FBPase inhibitors or that they have blood glucose lowering activity. Furthermore, lower alkyl phosphonic esters are not FBPase inhibitors and are not readily hydrolyzed into active compounds within the body.

European patent application EP 0 620 227 A1 discloses certain heterocycles including benzimidazoles having a diphosphonic acid where the X linker in formula 1 of the claims is alkylamino and alkylaminoalkyl. These compounds are said to inhibit bone resorption. There is no suggestion that the disclosed compounds were FBPase inhibitors or that they have blood glucose lowering activity.

German Offenlegungsschrift 2855659 discloses certain free phosphonic acids of benzimidazoles where A is amino and X is alkyl or alkene. These compounds are supposed to be corrosion inhibitors. There is no suggestion that the disclosed compounds were FBPase inhibitors or that they have blood glucose lowering activity.

Brief Description of the Drawings

FIG. 1 is a scheme depicting the eleven enzymes of the gluconeogenesis pathway.

FIG. 2 shows that compounds **12.61**, **12.53**, **12.52**, and **12.64** inhibit human liver FBPase activity *in vitro* in a dose dependent manner.

FIG. 3 shows that compound **12.1** and ZMP displaced AMP from human liver FBPase in a dose dependent manner.

FIG. 4 shows that compounds **12.1**, **12.53**, and **12.61** inhibit glucose production *in vitro* in rat hepatocytes.

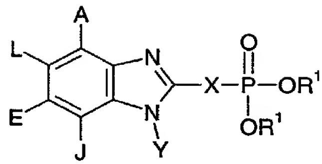
FIG. 5 shows the inhibition of glucose production and the accumulation of fructose-1,6-bisphosphate is dependent on the dose of compound **12.64**.

Summary of the Invention

The present invention is directed towards novel benzimidazole compounds which bind to the AMP site and are potent FBPase inhibitors. In another aspect, the present invention is directed to the preparation of these novel benzimidazole compounds and to the in vitro and in vivo FBPase inhibitory activity of these compounds. Another aspect of the present invention is directed to the clinical use of the novel FBPase inhibitors as a method of treatment or prevention of diseases responsive to inhibition of gluconeogenesis and in diseases responsive to lowered blood glucose levels.

The compounds are also useful in treating or preventing excess glycogen storage diseases and insulin dependent diseases such as cardiovascular diseases including atherosclerosis.

The invention comprises the novel benzimidazole analogs as specified below in formula 1. Also included in the scope of the present invention are prodrugs of the compounds of formula 1.



Formula 1

Since these compounds may have asymmetric centers, the present invention is directed not only to racemic mixtures of these compounds, but also to individual stereoisomers. The present invention also includes pharmaceutically acceptable and/or useful salts of the compounds of formula 1, including acid addition salts. The present inventions also encompass prodrugs of compounds of formula 1.

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted.

Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups and polycyclic or fused compounds such as optionally substituted naphthyl groups.

Heterocyclic aryl groups are groups having from 1 to 4 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Suitable heteroaryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, and the like, all optionally substituted.

The term "biaryl" represents aryl groups containing more than one aromatic ring including both fused ring systems and aryl groups substituted with other aryl groups.

The term "alicyclic" means compounds which combine the properties of aliphatic and cyclic compounds and include but are not limited to aromatic, cycloalkyl and bridged cycloalkyl compounds. The cyclic compound includes heterocycles. Cyclohexenylethyl, cyclohexanylethyl, and norbornyl are suitable alicyclic groups. Such groups may be optionally substituted.

The term "optionally substituted" or "substituted" includes groups substituted by one to four substituents, independently selected from lower alkyl, lower aryl, lower aralkyl, lower alicyclic, hydroxy, lower alkoxy, lower aryloxy, perhaloalkoxy, aralkoxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroaralkoxy, azido, amino, guanidino, halogen, lower alkylthio, oxa, ketone, carboxy esters, carboxyl, carboxamido, nitro, acyloxy, alkylamino, aminoalkyl, alkylaminoaryl, alkylaryl, alkylaminoalkyl, alkoxyaryl, arylamino, aralkylamino, phosphonate, sulfonate, carboxamidoalkylaryl, carboxamidoaryl, hydroxyalkyl, haloalkyl, alkylaminoalkylcarboxy, aminocarboxamidoalkyl, cyano, lower alkoxyalkyl, and lower perhaloalkyl.

The term "aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include benzyl, picolyl, and the like, and may be optionally substituted.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such as with up to and including 10, preferably up to and including 6, and advantageously one to four carbon atoms. Such groups may be straight chain, branched, or cyclic.

The terms "arylamino" (a), and "aralkylamino" (b), respectively, refer to the group -NRR' wherein respectively, (a) R is aryl and R' is hydrogen, alkyl, aralkyl or aryl, and (b) R is aralkyl and R' is hydrogen or aralkyl, aryl, alkyl.

The term "acyl" refers to -C(O)R where R is alkyl and aryl.

The term "carboxy esters" refers to -C(O)OR where R is alkyl, aryl, aralkyl, and alicyclic, all optionally substituted.

The term "oxa" refers to =O in an alkyl group.

The term "alkylamino" refers to -NRR' where R and R' are independently selected from hydrogen or alkyl.

The term "carbonylamine" or "carbonylamino" refers to $-CONR_2$ where each R is independently hydrogen or alkyl.

The term "halogen" or "halo" refers to -F, -Cl, -Br and -I.

The term "oxyalkylamino" refers to -O-alk-NR-, where "alk" is an alkylene group and R is H or alkyl.

The term “alkylsulfonate” refers to the group -alk-$S(O)_2$-O- where “alk” is an alkylene group.

The term “alkylaminoalkylcarboxy” refers to the group -alk-NR-alk-C(O)-O- where “alk” is an alkylene group, and R is a H or lower alkyl.

The term “alkylaminocarbonyl” refers to the group -alk-NR-C(O)- where “alk” is an alkylene group, and R is a H or lower alkyl.

The term “oxyalkyl” refers to the group -O-alk- where “alk” is an alkylene group.

The term “alkylcarboxyalkyl” refers to the group -alk-C(O)-O-alkyl where each alk is independently an alkylene group.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched chain and cyclic groups. Alkyl groups may be optionally substituted.

The term “bidentate” refers to an alkyl group that is attached by its terminal ends to the same atom to form a cyclic group. For example, propylene imine contains a bidentate propylene group.

The term “cyclic alkyl” refers to alkyl groups that are cyclic.

The term “heterocyclic” and “heterocyclic alkyl” refer to cyclic alkyl groups containing at least one heteroatom. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Heterocyclic groups may be attached through a heteroatom or through a carbon atom in the ring.

The term "alkenyl" refers to unsaturated groups which contain at least one carbon-carbon double bond and includes straight-chain, branched-chain and cyclic groups. Alkene groups may be optionally substituted.

The term "alkynyl" refers to unsaturated groups which contain at least one carbon-carbon triple bond and includes straight-chain, branched-chain and cyclic groups. Alkyne groups may be optionally substituted.

The term "alkylene" refers to a divalent straight chain, branched chain or cyclic saturated aliphatic radical.

The term “acyloxy” refers to the ester group -O-C(O)R, where R is H, alkyl, alkenyl, alkynyl, aryl, aralkyl, or alicyclic.

The term “alkylaryl” refers to the group -alk-aryl- where “alk” is an alkylene group. “Lower alkylaryl” refers to such groups where alkylene is lower alkyl.

The term “alkylamino” refers to the group -alk-NR- wherein “alk” is an alkylene group.

The term “alkyl(carboxyl)” refers to carboxyl substituted off the alkyl chain. Similarly, “alkyl(hydroxy)”, “alkyl(phosphonate)”, and “alkyl(sulfonate)” refers to substituents off the alkyl chain.

The term “alkylaminoalkyl” refers to the group -alk-NR-alk- wherein each “alk” is an independently selected alkylene, and R is H or lower alkyl. “Lower alkylaminoalkyl” refers to groups where each alkylene group is lower alkyl.

The term “alkylaminoaryl” refers to the group -alk-NR-aryl- wherein “alk” is an alkylene group. In “lower alkylaminoaryl”, the alkylene group is lower alkyl.

The term “alkyloxyaryl” refers to an alkylene group substituted with an aryloxy group. In “lower alkyloxyaryl”, the alkylene group is lower alkyl.

The term “alkylacylamino” refers to the group -alk-N-(COR)- wherein alk is alkylene and R is lower alkyl. In “lower alkylacylamino”, the alkylene group is lower alkyl.

The term “alkoxyalkylaryl” refers to the group -alk-O-alk-aryl- wherein each “alk” is independently an alkylene group. “Lower aloxyalkylaryl” refers to such groups where the alkylene group is lower alkyl.

The term “alkylacylaminoalkyl refers to the group -alk-N-(COR)-alk- where each alk is an independently selected alkylene group. In “lower alkylacylaminoalkyl” the alkylene groups are lower alkyl.

The term “alkoxy” refers to the group -alk-O- wherein alk is an alkylene group.

The term “alkoxyalkyl” refers to the group -alk-O-alk- wherein each alk is an independently selected alkylene group. In “lower alkoxyalkyl”, each alkylene is lower alkyl.

The term “alkylthio” refers to the group -alk-S- wherein alk is alkylene group.

The term “alkylthioalkyl” refers to the group -alk-S-alk- wherein each alk is an independently selected alkylene group. In “lower alkylthioalkyl” each alkylene is lower alkylene.

The term “aralkylamino” refers to an amine substituted with an aralkyl group.

The term “alkylcarboxamido” refers to the group -alk- C(O)N(R)- wherein alk is an alkylene group and R is H or lower alkyl.

The term “alkylcarboxamidoalkyl” refers to the group -alk-C(O)N(R)-alk- wherein each alk is an independently selected alkylene group and R is lower alkyl. In “lower alkylcarboxamidoalkyl” each alkylene is lower alkyl.

The term “alkylcarboxamidoalkylaryl” refers to the group -alk_1-C(O)-NH-alk_2Ar- wherein alk_1 and alk_2 are independently selected alkylene groups and alk_2 is substituted with an aryl group, Ar. In “lower alkylcarboxamidoalkylaryl”, each alkylene is lower alkyl.

The term “heteroalicyclic” refers to an alicyclic group having 1 to 4 heteroatoms selected from nitrogen, sulfur, phosphorus and oxygen.

The term “aminocarboxamidoalkyl” refers to the group -NH-C(O)-N(R)-R wherein each R is an independently selected alkyl group. “Lower aminocaboxamidoalkyl” refers to such groups wherein each R is lower alkyl.

The term “heteroarylalkyl” refers to an alkyl group substituted with a heteroaryl group.

The term “perhalo” refers to groups wherein every C-H bond has been replaced with a C-halo bond on an aliphatic or aryl group. Suitable perhaloalkyl groups include -CF_3 and -$CFCl_2$.

The term “guanidine” refers to both -NR-C(NR)-NR_2 as well as -N=C$(NR_2)_2$ where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

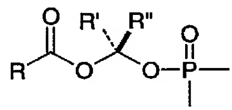
The term “amidine” refers to -C(NR)-NR_2 where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

The term "pharmaceutically acceptable salt" includes salts of compounds of formula 1 and its prodrugs derived from the combination of a compound of this invention and an organic or inorganic acid or base.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the "drug" substance either as a result of spontaneous chemical reaction(s) or by enzyme catalyzed or metabolic reaction(s). Reference is made to various prodrugs such as acyl esters, carbonates, and carbamates, included herein. The groups illustrated are exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of formula 1, fall within the scope of the present invention.

The term "prodrug ester" as employed herein includes, but is not limited to, the following groups and combinations of these groups:

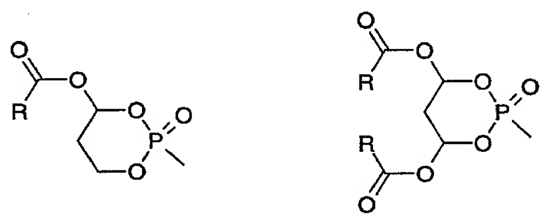
[1] Acyloxyalkyl esters which are well described in the literature (Farquhar et al., J. Pharm. Sci. 72, 324-325 (1983)) and are represented by formula A



Formula A

wherein R, R', and R" are independently H, alkyl, aryl, alkylaryl, and alicyclic; (see WO 90/08155; WO 90/10636).

[2] Other acyloxyalkyl esters are possible in which an alicyclic ring is formed such as shown in formula B. These esters have been shown to generate phosphorus-containing nucleotides inside cells through a postulated sequence of reactions beginning with deesterification and followed by a series of elimination reactions (e.g. Freed et al., Biochem. Pharm. 38: 3193-3198 (1989)).

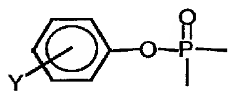


Formula B

wherein R is -H, alkyl, aryl, alkylaryl, alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, cycloalkyl, or alicyclic.

[3] Another class of these double esters known as alkyloxycarbonyloxymethyl esters, as shown in formula A, where R is alkoxy, aryloxy, alkylthio, arylthio, alkylamino, and arylamino; R', and R" are independently H, alkyl, aryl, alkylaryl, and alicyclic, have been studied in the area of β-lactam antibiotics (Tatsuo Nishimura et al. *J. Antibiotics*, **1987**, *40(1)*, 81-90; for a review see Ferres, H., *Drugs of Today*, **1983**, *19*, 499.). More recently Cathy, M. S., et al. (Abstract from AAPS Western Regional Meeting, April, **1997**) showed that these alkyloxycarbonyloxymethyl ester prodrugs on (9-[(R)-2-phosphonomethoxy)propyl]adenine (PMPA) are bioavailable up to 30% in dogs.

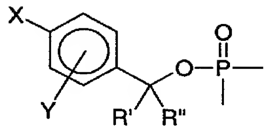
[4] Aryl esters have also been used as phosphonate prodrugs (*e.g.* Erion, DeLambert et al., J. Med. Chem. 37: 498, 1994; Serafinowska et al., J. Med. Chem. 38: 1372, 1995). Phenyl as well as mono and poly-substituted phenyl proesters have generated the parent phosphonic acid in studies conducted in animals and in man (Formula C). Another approach has been described where Y is a carboxylic ester ortho to the phosphate. Khamnei and Torrence, J. Med. Chem.; 39:4109-4115 (1996).



Formula C

wherein Y is H, alkyl, aryl, alkylaryl, alkoxy, acetoxy, halogen, amino, alkoxycarbonyl, hydroxy, cyano, alkylamino, and alicyclic.

[5] Benzyl esters have also been reported to generate the parent phosphonic acid. In some cases, using substituents at the para-position can accelerate the hydrolysis. Benzyl analogs with 4-acyloxy or 4-alkyloxy group [Formula D, X = H, OR or O(CO)R or O(CO)OR] can generate the 4-hydroxy compound more readily through the action of enzymes, *e.g.* oxidases, esterases, etc. Examples of this class of prodrugs are described in Mitchell et al., J. Chem. Soc. Perkin Trans. I 2345 (1992); Brook, et al. WO 91/19721.



Formula D

wherein X and Y are independently H, alkyl, aryl, alkylaryl, alkoxy, acetoxy, hydroxy, cyano, nitro, perhaloalkyl, halo, or alkyloxycarbonyl; and

R' and R" are independently H, alkyl, aryl, alkylaryl, halogen, and alicyclic.

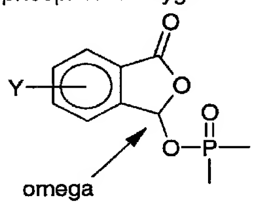
[6] Thio-containing phosphonate proesters have been described that are useful in the delivery of FBPase inhibitors to hepatocytes. These proesters contain a protected thioethyl moiety as shown in formula E. One or more of the oxygens of the phosphonate can be esterified. Since the mechanism that results in de-esterification requires the generation of a free thiolate, a variety of thiol protecting groups are possible. For example, the disulfide is reduced by a reductase-mediated process (Puech et al., Antiviral Res., 22: 155-174 (1993)). Thioesters will also generate free thiolates after esterase-mediated hydrolysis. Benzaria, et al., J. Med. Chem., 39:4958 (1996). Cyclic analogs are also possible and were shown to liberate phosphonate in isolated rat hepatocytes. The cyclic disulfide shown below has not been previously described and is novel.

Formula E

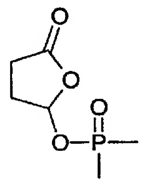
wherein Z is alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, or alkylthio.

Other examples of suitable prodrugs include proester classes exemplified by Biller and Magnin (U.S. Patent No. 5,157,027); Serafinowska et al. (J. Med. Chem. 38, 1372 (1995)); Starrett et al. (J. Med. Chem. 37, 1857

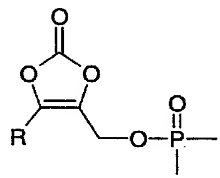
(1994)); Martin et al. J. Pharm. Sci. 76, 180 (1987); Alexander et al., Collect. Czech. Chem. Commun, 59, 1853 (1994)); and EPO patent application 0 632 048 A1. Some of the structural classes described are optionally substituted, including fused lactones attached at the omega position and optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen such as:



3-phthalidyl



2-oxotetrahydrofuran-5-yl

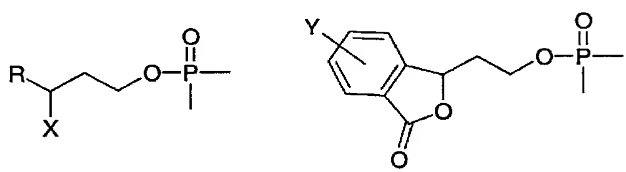


2-oxo-4,5-didehydro-1,3-dioxolanemethyl

wherein R is -H, alkyl, cycloalkyl, or alicyclic; and

wherein Y is -H, alkyl, aryl, alkylaryl, cyano, alkoxy, acetoxy, halogen, amino, alkylamino, alicyclic, and alkoxycarbonyl.

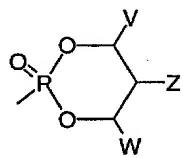
[7] Propyl phosphonate proesters can also be used to deliver FBPase inhibitors into hepatocytes. These proesters may contain a hydroxyl and hydroxyl group derivatives at the 3-position of the propyl group as shown in formula F. The R and X groups can form a cyclic ring system as shown in formula F. One or more of the oxygens of the phosphonate can be esterified.



Formula F

wherein R is alkyl, aryl, heteroaryl;
X is hydrogen, alkylcarbonyloxy, alkyloxycarbonyloxy; and
Y is alkyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, halogen, hydrogen, hydroxy, acetoxy, amino.

[8] The cyclic propyl phosphonate esters as in Formula G are shown to activate to phosphonic acids. The activation of prodrug can be mechanistically explained by *in vivo* oxidation and elimination steps. These prodrugs inhibit glucose production in isolated rat hepatocytes and are also shown to deliver FBPase inhibitors to the liver following oral administration.



Formula G

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

[9] Phosphoramidate derivatives have been explored as potential phosphonate prodrugs (e.g. McGuigan et al., *Antiviral Res.* **1990,** *14*: 345; **1991,** *15* : 255. Serafinowska et al., *J. Med. Chem.*, **1995**, *38*, 1372). Most phosphoramidates are unstable under aqueous acidic conditions and are hydrolyzed to the corresponding phosphonic acids. Cyclic phosphoramidates have also been studied as phosphonate prodrugs because of their potential for greater stability compared to non cyclic phosphoramidates (e.g. Starrett et al., *J. Med. Chem.*, **1994,** *37*: 1857).

Other prodrugs are possible based on literature reports such as substituted ethyls for example, bis(trichloroethyl)esters as disclosed by McGuigan, et al. Bioorg Med. Chem. Lett., 3:1207-1210 (1993), and the phenyl and benzyl combined nucleotide esters reported by Meier, C. et al. Bioorg. Med. Chem. Lett., 7:99-104 (1997).

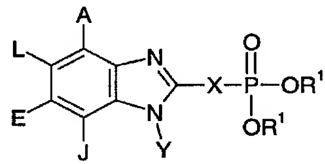
X group nomenclature as used herein in formula 1 describes the group attached to the phosphonate and ends with the group attached to the 2-position of the benzimidazole ring. For example, when X is alkylamino, the following structure is intended:

$$\text{(benzimidazole ring)-NR-alk-P(O)(OR}^1)_2$$

Y group nomenclature likewise ends with the group attached to the ring.

DETAILED DESCRIPTION OF THE INVENTION

Preferred compounds of the present invention are inhibitors of the AMP site of FBPase of the following formula 1:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

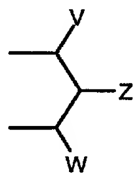
J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$,

$-NR^2$-C(O)-R^3, -C(R^2)$_2$- OC(O)R^3, C(R^2)$_2$-O-C(O)OR^3, -C(R^2)$_2$OC(O)SR^3, alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are


,

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R^9; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, -CH(Ar)OH, -CH(CH=CR^2R^2)OH, -CH(C≡CR^2)OH, and -R^2;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is -R^2, then at least one of V and W is not -H or -R^9;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof; with the provisos that:

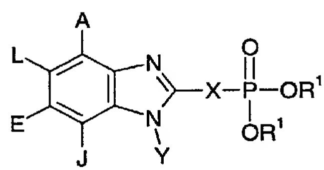
a) R^1 is not lower alkyl of 1-4 carbon atoms;

b) when X is alkyl or alkene, then A is $-N(R^8{}_2)$;

c) X is not alkylamine and alkylaminoalkyl substituted with phosphonic esters and acids; and

d) A, L, E, J, Y, and X together may only form 0-2 cyclic groups.

Preferred compounds for the method of use claims are inhibitors of the AMP site of FBPase of the following formula 1:



wherein:

A, E, and L are selected from the group consisting of $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl,

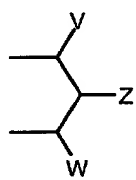
perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



,

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

Preferred Compounds of Formula 1

Suitable alkyl groups include groups having from 1 to about 20 carbon atoms. Suitable aryl groups include groups having from 1 to about 20 carbon atoms. Suitable aralkyl groups include groups having from 2 to about 21 carbon atoms. Suitable acyloxy groups include groups having from 1 to about 20 carbon atoms. Suitable alkylene groups include groups having from 1 to about 20 carbon atoms. Suitable alicyclic groups include groups having 3 to about 20 carbon atoms. Suitable heteroaryl groups include groups having from 1 to about 20 carbon atoms and from 1 to 5 heteroatoms, preferably independently selected from nitrogen, oxygen, phosphorous, and sulfur. Suitable heteroalicyclic groups include groups having from 2 to about twenty carbon atoms and from 1 to 5 heteroatoms, preferably independently selected from nitrogen, oxygen, phosphorous, and sulfur.

Preferred A, L, and E groups include -H, $-NR^8_2$, $-NO_2$, hydroxy, alkylaminocarbonyl, halogen, $-OR^7$, $-SR^7$, lower perhaloalkyl, and C1-C5 alkyl, or together E and J form a cyclic group. Such a cyclic group may be aromatic, cyclic alkyl, or heterocyclic alkyl, and may be optionally substituted. Suitable aromatic groups include thiazole. Particularly preferred A, L and E groups are $-NR^8_2$, -H, hydroxy, halogen, lower alkoxy, lower perhaloalkyl, and lower alkyl.

Preferred A groups include, $-NR^8_2$, -H, halogen, lower perhaloalkyl, and lower alkyl.

Preferred L and E groups include -H, lower alkoxy, lower alkyl, and halogen.

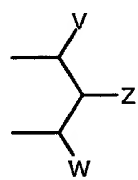
Preferred J groups include -H, halogen, lower alkyl, lower hydroxylalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower perhaloalkyl, lower alkenyl, lower alkynyl, lower aryl, heterocyclic, and alicyclic, or together with Y forms a cyclic group. Such a cyclic group may be aromatic, cyclic alkyl, or heterocyclic, and may be optionally substituted. Particularly preferred J groups include -H, halogen, and lower alkyl, lower hydroxyalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower alkenyl, alicyclic, and aryl. Especially preferred are alicyclic and lower alkyl.

Preferred X groups include alkyl, alkynyl, aryl, alkoxyalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, 1,1-dihaloalkyl, carbonylalkyl, alkyl(OH), and alkyl(sulfonate). Particularly preferred is heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, alkyl(sulfonate), and alkoxyalkyl. Also particularly preferred are heteroaryl, alkylaminocarbonyl, and alkoxyalkyl. Especially preferred are methylaminocarbonyl, methoxymethyl, and furanyl.

In one preferred aspect X is not substituted with a phosphonic acid or ester. In another preferred aspect, when X is substituted with a phosphonic acid or ester, then A is $-N(R^8)_2$ and Y is not -H. In another preferred aspect, when X is aryl or alkylaryl, these groups are not linked 1,4 through a 6-membered aromatic ring.

Preferred Y groups include -H, alkyl, aralkyl, aryl, and alicyclic, all except -H may be optionally substituted. Particularly preferred are lower alkyl, and alicyclic.

Preferred R^1 groups include -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted phenyl, optionally substituted benzyl, optionally substituted alkylaryl, $-C(R^2)_2OC(O)R^3$, $C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2$-OC(O)SR^3, -alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxyl, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are alkyl-S-S-alkyl to form a cyclic group, or R^1 and R^1 together are



,

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,

alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

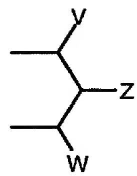
R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

Preferred such R^1 groups include optionally substituted phenyl, optionally substituted benzyl, -H, and $-C(R^2)_2OC(O)R^3$. Also preferred are such groups where at least one R^1 is aryl or-$C(R^2)_2$ aryl. Particularly preferred is H. Also preferred is when at least one R^1 is alkyl, preferably greater than 4 carbon atoms. Another preferred aspect is when at least one R^1 is $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-OC(O)OR^3$, $-C(R^2)_2-OC(O)SR^3$. Also particularly preferred is when R^1 and R^1 together are optionally substituted, including fused, lactones attached at the omega position or are optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen. Also preferred is when at least one R^1 is -alkyl-S-S-alkylhydroxyl, -alkyl-S-C(O)R^3, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group. Also preferred is

where R^1 and R^1 together are



to form a cyclic group,

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

Particularly preferred are such groups wherein V and W both form a 6-membered carbocyclic ring substituted with 0-4 groups, selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, and alkoxy; and Z is $-R^2$. Also particularly preferred are such groups wherein V and W are hydrogen; and Z is selected from the group consisting of hydroxyalkyl, acyloxyalkyl,

alkyloxyalkyl, and alkoxycarboxyalkyl. Also particularly preferred are such groups wherein V and W are independently selected from the group consisting of hydrogen, optionally substituted aryl, and optionally substituted heteroaryl, with the proviso that at least one of V and W is optionally substituted aryl or optionally substituted heteroaryl.

Also particularly preferred are such compounds where R^1 is alicyclic where the cyclic moiety contains carbonate or thiocarbonate.

Preferred R^4 and R^7 groups include -H, and lower alkyl.

In one preferred aspect A, L, and E are independently -H, lower alkyl, hydroxy, halogen, lower alkoxy, lower perhaloalkyl, and $-NR^8{}_2$; X is aryl, alkoxyalkyl, alkyl, alkylthio, 1,1-dihaloalkyl, carbonylalkyl, alkyl(hydroxy), alkyl(sulfonate), alkylaminocarbonyl, and alkylcarbonylamino; and each R^4 and R^7 is independently -H, and lower alkyl. Particularly preferred are such compounds where A, L, and E are independently -H, lower alkyl, halogen, and $-NR^8{}_2$; J is -H, halogen, haloalkyl, hydroxyalkyl, $R^8{}_2N$-alkyl, lower alkyl, lower aryl, heterocyclic, and alicyclic, or together with Y forms a cyclic group; and X is heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, and alkoxyalkyl. Especially preferred are such compounds where A is -H, $-NH_2$, -F, and $-CH_3$, L is -H, -F, $-OCH_3$, -Cl, and $-CH_3$, E is -H and -Cl, J is -H, halo, C1-C5 hydroxyalkyl, C1-C5 haloalkyl, C1-C5 $R^8{}_2N$-alkyl, C1-C5 alicyclic, and C1-C5 alkyl, X is $-CH_2OCH_2-$, and 2,5-furanyl, and Y is lower alkyl. Most preferred are the following such compounds and their salts, and prodrug and their salts:

1) A is $-NH_2$, L is -F, E is -H, J is -H, Y is isobutyl, and X is 2,5-furanyl;

2) A, L, and J are -H, E is -Cl, Y is isobutyl, and X is 2,5-furanyl;

3) A is $-NH_2$, L is -F, E and J are -H, Y is cyclopropylmethyl, and X is 2,5-furanyl;

4) A is $-NH_2$, L is -F, E is -H, J is ethyl, Y is isobutyl, and X is 2,5-furanyl;

5) A is $-CH_3$, L is -Cl, E and J are -H, Y is isobutyl, and X is 2,5-furanyl;

6) A is $-NH_2$, L is -F, E is -H, J is -Cl, Y is isobutyl, and X is 2,5-furanyl;

7) A is $-NH_2$, L is -F, E is -H, J is -Br, Y is isobutyl, and X is $-CH_2OCH_2$; and

8) A, L, E, and J are $-CH_3$, Y is cyclopropylmethyl, and X is 2,5-furanyl.

Also especially preferred are compounds where A is $-NH_2$, L is -F, E is -H, J is bromopropyl, bromobutyl, chlorobutyl, cyclopropyl, hydroxypropyl, or N,N-dimethylaminopropyl, and X is 2,5-furanyl. The preferred prodrug is where R^1 is pivaloyloxymethyl or its HCl salt.

In the following examples of preferred compounds, the following prodrugs are preferred:

Acyloxyalkyl esters;
Alkoxycarbonyloxyalkyl esters;
Aryl esters;
Benzyl and substituted benzyl esters;
Disulfide containing esters;
Substituted (1,3-dioxolen-2-one)methyl esters;
Substituted 3-phthalidyl esters;
Cyclic-[2'-hydroxymethyl]-1,3-propanyl diesters and hydroxy protected forms;
Lactone type esters; and all mixed esters resulted from possible combinations of above esters.
Bis-pivaloyloxymethyl esters;
Bis-isobutyryloxymethyl esters;
Cyclic-[2'-hydroxymethyl]-1,3-propanyl diester;
Cyclic-[2'-acetoxymethyl]-1,3-propanyl diester;
Cyclic-[2'-methyloxycarbonyloxymethyl]-1,3-propanyl diester;
Bis-benzoylthiomethyl esters;
Bis-benzoylthioethyl esters;
Bis-benzoyloxymethyl esters;
Bis-*p*-fluorobenzoyloxymethyl esters;
Bis-6-chloronicotinoyloxymethyl esters;
Bis-5-bromonicotinoyloxymethyl esters;
Bis-thiophenecarbonyloxymethyl esters;
Bis-2-furoyloxymethyl esters;
Bis-3-furoyloxymethyl esters;
Diphenyl esters;
Bis-(4-methoxyphenyl) esters;
Bis-(2-methoxyphenyl) esters;
Bis-(2-ethoxyphenyl) esters;
Mono-(2-ethoxyphenyl) esters;
Bis-(4-acetamidophenyl) esters;

Bis-(4-aceyloxyphenyl) esters;
Bis-(4-hydroxyphenyl) esters;
Bis-(2-acetoxyphenyl) esters;
Bis-(3-acetoxyphenyl) esters;
Bis-(4-morpholinophenyl) esters;
Bis-[4-(1-triazolophenyl) esters;
Bis-(3-*N,N*-dimethylaminophenyl) esters;
Bis-(2-tetrahydronapthyl) esters;
Bis-(3-chloro-4-methoxy)benzyl esters;
Bis-(3-bromo-4-methoxy)benzyl esters;
Bis-(3-cyano-4-methoxy)benzyl esters;
Bis-(3-chloro-4-acetoxy)benzyl esters;
Bis-(3-bromo-4-acetoxy)benzyl esters;
Bis-(3-cyano-4-acetoxy)benzyl esters;
Bis-(4-chloro)benzyl esters;
Bis-(4-acetoxy)benzyl esters;
Bis-(3,5-dimethoxy-4-acetoxy)benzyl esters;
Bis-(3-methyl-4-acetoxy)benzyl esters;
Bis-(benzyl)esters;
Bis-(3-methoxy-4-acetoxy)benzyl esters;
Bis-(3-chloro-4-acetoxy)benzyl esters;
cyclic-(2,2-dimethylpropyl)phosphonoamidate;
cyclic-(2-hydroxymethylpropyl) ester;
Bis-(6'-hydroxy-3',4'-disulfide)hexyl esters;
Bis-(6'-acetoxy-3',4'-disulfide)hexyl esters;
(3',4'-Dithia)cyclononane esters;
Bis-(5-methyl-1,3-dioxolen-2-one-4-yl)methyl esters;
Bis-(5-ethyl-1,3-dioxolen-2-one-4-yl)methyl esters;
Bis-(5-tert-butyl-1,3-dioxolen-2-one-4-yl)methyl esters;
Bis-3-(5,6,7-trimethoxy)phthalidyl esters;
Bis-(cyclohexyloxycarbonyloxymethyl) esters;
Bis-(isopropyloxycarbonyloxymethyl) esters;
Bis-(ethyloxycarbonyloxymethyl) esters;
Bis-(methyloxycarbonyloxymethyl) esters;
Bis-(isopropylthiocarbonyloxymethyl) esters;
Bis-(phenyloxycarbonyloxymethyl) esters;

Bis-(benzyloxycarbonyloxymethyl) esters;
Bis-(phenylthiocarbonyloxymethyl) esters;
Bis-(*p*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*m*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methylphenyloxycarbonyloxymethyl) esters;
Bis-(*p*-chlorophenyloxycarbonyloxymethyl) esters;
Bis-(1,4-biphenyloxycarbonyloxymethyl) esters;
Bis-[(2-phthalimidoethyl)oxycarbonyloxymethyl]esters;
Bis-(*N*-Phenyl, *N*-methylcarbamoyloxymethyl) esters;
Bis-(2-trichloroethyl) esters;
Bis-(2-bromoethyl) esters;
Bis-(2-iodoethyl) esters;
Bis-(2-azidoethyl) esters;
Bis-(2-acetoxyethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-(2-*N,N*-diaminoethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-(methoxycarbonylmethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-[*N,N*-di(2-hydroxyethyl)]amidomethylesters;
Bis-(2-aminoethyl) esters;
Bis-(2-methyl-5-thiozolomethyl) esters;
Bis-(bis-2-hydroxyethylamidomthyl) esters.

Most preferred are the following:

Bis-pivaloyloxymethyl esters;
Bis-isobutyryloxymethyl esters;
cyclic-(2-hydroxymethylpropyl) ester;
cyclic-(2-acetoxymethylpropyl) ester;
cyclic-(2-methyloxycarbonyloxymethylpropyl) ester;
cyclic-(2-cyclohexylcarbonyloxymethylpropyl)ester;
cyclic-(2-aminomethylpropyl)ester;
cyclic-(2-azidomethylpropyl)ester;
Bis-benzoylthiomethyl esters;

Bis-benzoylthioethylesters;
Bis-benzoyloxymethyl esters;
Bis-*p*-fluorobenzoyloxymethyl esters;
Bis-6-chloronicotinoyloxymethyl esters;
Bis-5-bromonicotinoyloxymethyl esters;
Bis-thiophenecarbonyloxymethyl esters;
Bis-2-furoyloxymethyl esters;
Bis-3-furoyloxymethyl esters;
Diphenyl esters;
Bis-(2-methyl)phenyl esters;
Bis-(2-methoxy)phenyl esters;
Bis-(2-ethoxy)phenyl esters;
Bis-(4-methoxy)phenyl esters;
Bis-(3-bromo-4-methoxy)benzyl esters;
Bis-(4-acetoxy)benzyl esters;
Bis-(3,5-dimethoxy-4-acetoxy)benzyl esters;
Bis-(3-methyl-4-acetoxy)benzyl esters;
Bis-(3-methoxy-4-acetoxy)benzyl esters;
Bis-(3-chloro-4-acetoxy)benzyl esters;
Bis-(cyclohexyloxycarbonyloxymethyl) esters;
Bis-(isopropyloxycarbonyloxymethyl) esters;
Bis-(ethyloxycarbonyloxymethyl) esters;
Bis-(methyloxycarbonyloxymethyl) esters;
Bis-(isopropylthiocarbonyloxymethyl) esters;
Bis-(phenyloxycarbonyloxymethyl) esters;
Bis-(benzyloxycarbonyloxymethyl) esters;
Bis-(phenylthiocarbonyloxymethyl) esters;
Bis-(*p*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*m*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methoxyphenyloxycarbonyloxymethyl) esters;
Bis-(*o*-methylphenyloxycarbonyloxymethyl) esters;
Bis-(*p*-chlorophenyloxycarbonyloxymethyl) esters;
Bis-(1,4-biphenyloxycarbonyloxymethyl) esters;
Bis-[(2-phthalimidoethyl)oxycarbonyloxymethyl]esters;
Bis-(6'-hydroxy-3',4'-disulfide)hexyl esters; and
(3',4'-Disulfide)cyclononane esters.

Bis-(2-bromoethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-(2-*N,N*-diaminoethyl) esters;

Examples of preferred compounds include, but are not limited to the salts and prodrugs of the compounds of Table 1.

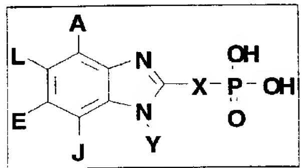


Table Compound No.	Synthetic Example No.	A	L	E	J[1]	Y	X[2]
1	12.2	NH2	H	H	H	cyclohexylethyl	2,5-furanyl
2	12.3	NH2	H	H	H	H	2,5-furanyl
3	12.4	NH2	H	H	H	methyl	2,5-furanyl
4	12.5	NH2	H	H	H	4-methylbenzyl	2,5-furanyl
5	12.6	NH2	H	H	H	3-CO2Me benzyl	2,5-furanyl
6	12.1	NH2	H	H	H	Et	2,5-furanyl
7	12.8	NH2	H	H	H	Et	methoxymethyl
8	12.9	NH2	H	H	H	3-methylbenzyl	2,5-furanyl
9	12.10	NH2	H	H	H	2-(3-CO2Et-5,6,7,8-tetrahydronapthyl	2,5-furanyl
10	12.11	NH2	H	H	H	2-(3-CO2H-5,6,7,8-tetrahydronapthyl	2,5-furanyl
11	12.12	NH2	H	H	H	propyl	2,5-furanyl
12	12.13	NH2	H	H	H	norbornylmethyl	2,5-furanyl

[1] In the Table for J where structures are depicted, the line on the left side is a direct attachment to the benzimidazole ring.

[2] In the table for X where structures are depicted, the line on the left side is part of the benzimidazole ring, an atom or the left side is attached to the benzimidazole ring, and the line on the right side is attached directly to the P of the phosphonate.

13	12.14	NH2	H	H	H	3-CO2H benzyl	2,5-furanyl
14	12.15	NH2	H	H	H	cyclopentylmethyl	2,5-furanyl
15	12.16	NH2	H	H	H	cyclopropanemethyl	2,5-furanyl
16	12.17	NH2	H	H	H	cyclobutylmethyl	2,5-furanyl
17	12.18	NH2	H	H	H	3-methyl-6, 6-dimethyl-2-cyclohexenylmethyl	2,5-furanyl
18	12.19	NH2	H	H	H	2-methyl-2-butenyl	2,5-furanyl
19	12.20	NH2	H	H	H	1S,2S,5S-myrtanyl	2,5-furanyl
20	12.21	NH2	H	H	H	4-tBu benzyl	2,5-furanyl
21	12.22	NH2	H	H	H	cyclohexylbutyl	2,5-furanyl
22	12.23	NH2	H	H	H	cyclohexylpropyl	2,5-furanyl
23	12.24	NH2	H	H	H	3-carboxypropyl	2,5-furanyl
24	12.25	NH2	H	H	H	3-CO2Et propyl	2,5-furanyl
25	12.26	NH2	H	H	H	tBu-methylketone	2,5-furanyl
26	12.27	NH2	H	H	H	cycloheptylmethyl	2,5-furanyl
27	12.28	NH2	H	H	H	cyclohexanylmethyl	2,5-furanyl
28	12.29	NH2	H	H	H	benzyl	2,5-furanyl
29	12.30	NH2	H	H	H	3-CF3-benzyl	2,5-furanyl
30	12.31	NH2	H	H	H	3-carbamoylpropyl	2,5-furanyl
31	12.32	NH2	H	H	H	7-hydroxy-3R, 7-dimethyloctyl	2,5-furanyl
32	12.33	NH2	H	H	H	4-chlorobutyl	2,5-furanyl
33	12.34	NH2	H	H	H	4-Ph-benzyl	2,5-furanyl
34	12.35	NH2	H	H	H	3-chloropropyl	2,5-furanyl
35	12.36	NH2	H	H	H	4-hydroxybutyl	2,5-furanyl
36	12.37	NH2	H	H	H	3-furanylmethyl	2,5-furanyl
37	12.38	NH2	H	H	H	3-OH-benzyl	2,5-furanyl
38	12.39	NH2	H	H	H	2-OMe-phenethyl	2,5-furanyl
39	12.40	NH2	H	H	H	3-OMe-phenethyl	2,5-furanyl
40		Me	Cl	H	H	ethyl	2,5-furanyl
41	12.46	NH2	H	H	Br	isobutyl	2,5-furanyl
42	12.47	NH2	H	H	Br	cyclobutylmethyl	2,5-furanyl
43	12.48	NH2	Br	H	H	cyclobutylmethyl	2,5-furanyl

44	12.51	NH2	H	H	H	2-thienylethyl	2,5-furanyl
45	12.52	NH2	Et	H	H	isobutyl	2,5-furanyl
46	12.56	NH2	H	H	H	3-NH2-phenethyl	2,5-furanyl
47	12.57	NH2	H	H	H	2-Et-pentyl	methoxymethyl
48	12.59	NH2	H	H	H	H	2,5-furanyl
49	12.60	NH2	Pr	H	H	isobutyl	2,5-furanyl
50		NH2	Et	H	H	isobutyl	2,5-furanyl
51	12.62	NH2	F	H	Br	isobutyl	2,5-furanyl
52	12.53	NH2	F	H	H	isobutyl	2,5-furanyl
53	12.64	NH2	F	H	Et	isobutyl	2,5-furanyl
54	12.54	NH2	F	H	Cl	isobutyl	2,5-furanyl
55		NH2	F	H	Me	isobutyl	2,5-furanyl
56		NH2	F	H	Pr	isobutyl	2,5-furanyl
57		NH2	F	H	i-Pr	isobutyl	2,5-furanyl
58		NH2	F	H	Bu	isobutyl	2,5-furanyl
59		NH2	F	H	i-Bu	isobutyl	2,5-furanyl
60		NH2	F	H	OMe	isobutyl	2,5-furanyl
61		NH2	F	H	OEt	isobutyl	2,5-furanyl
62		NH2	F	H	SMe	isobutyl	2,5-furanyl
63		NH2	F	H	SEt	isobutyl	2,5-furanyl
64		NH2	F	H	NEt2	isobutyl	2,5-furanyl
65		NH2	F	H	NMe2	isobutyl	2,5-furanyl
66		NH2	F	H	I	isobutyl	2,5-furanyl
67		NH2	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
68		NH2	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
69		NH2	F	H	p-F Phenyl	isobutyl	2,5-furanyl
70		NH2	F	H	o-F Phenyl	isobutyl	2,5-furanyl
71		NH2	F	H	m-F Phenyl	isobutyl	2,5-furanyl
72		NH2	F	H	2-Furanyl	isobutyl	2,5-furanyl
73		NH2	F	H	2-thiophenyl	isobutyl	2,5-furanyl
74		NH2	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
75		NH2	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
76		NH2	F	H	CN	isobutyl	2,5-furanyl
77		NH2	F	H	m-Cl phenyl	isobutyl	2,5-furanyl

78		NH2	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
79		NH2	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
80		NH2	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
81		NH2	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
82		NH2	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
83		NH2	F	H	CF3	isobutyl	2,5-furanyl
84		NH2	F	H	cyclopentyl	isobutyl	2,5-furanyl
85		NH2	F	H	cyclohexyl	isobutyl	2,5-furanyl
86		NH2	F	H	cyclobutyl	isobutyl	2,5-furanyl
87		NH2	F	H	cyclopropyl	isobutyl	2,5-furanyl
88		NH2	F	H	Phenyl	isobutyl	2,5-furanyl
89		NH2	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
90		NH2	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
91		NH2	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
92		NH2	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
93		NH2	F	Cl	F	isobutyl	2,5-furanyl
94		NH2	F	Cl	Me	isobutyl	2,5-furanyl
95		NH2	F	Cl	Pr	isobutyl	2,5-furanyl
96		NH2	F	Cl	i-Pr	isobutyl	2,5-furanyl
97		NH2	F	Cl	Bu	isobutyl	2,5-furanyl
98		NH2	F	Cl	i-Bu	isobutyl	2,5-furanyl
99		NH2	F	Cl	OMe	isobutyl	2,5-furanyl
100		NH2	F	Cl	OEt	isobutyl	2,5-furanyl
101		NH2	F	Cl	SMe	isobutyl	2,5-furanyl
102		NH2	F	Cl	SEt	isobutyl	2,5-furanyl
103		NH2	F	Cl	NEt2	isobutyl	2,5-furanyl
104		NH2	F	Cl	NMe2	isobutyl	2,5-furanyl
105		NH2	F	Cl	I	isobutyl	2,5-furanyl
106		NH2	F	Cl	m-OMePhenyl	isobutyl	2,5-furanyl
107		NH2	F	Cl	o-OMePhenyl	isobutyl	2,5-furanyl
108		NH2	F	Cl	p-F Phenyl	isobutyl	2,5-furanyl
109		NH2	F	Cl	o-F Phenyl	isobutyl	2,5-furanyl
110		NH2	F	Cl	m-F Phenyl	isobutyl	2,5-furanyl
111		NH2	F	Cl	2-Furanyl	isobutyl	2,5-furanyl

112		NH2	F	Cl	2-thiophenyl	isobutyl	2,5-furanyl
113		NH2	F	Cl	2-Furanylmethyl	isobutyl	2,5-furanyl
114		NH2	F	Cl	2-Thiophenylmethyl	isobutyl	2,5-furanyl
115		NH2	F	Cl	CN	isobutyl	2,5-furanyl
116		NH2	F	Cl	m-Cl phenyl	isobutyl	2,5-furanyl
117		NH2	F	Cl	p-Cl phenyl	isobutyl	2,5-furanyl
118		NH2	F	Cl	o-Cl phenyl	isobutyl	2,5-furanyl
119		NH2	F	Cl	m-Br Phenyl	isobutyl	2,5-furanyl
120		NH2	F	Cl	p-Br Phenyl	isobutyl	2,5-furanyl
121		NH2	F	Cl	o-Br Phenyl	Isobutyl	2,5-furanyl
122		NH2	F	Cl	CF3	isobutyl	2,5-furanyl
123		NH2	F	Cl	cyclopentyl	isobutyl	2,5-furanyl
124		NH2	F	Cl	cyclohexyl	isobutyl	2,5-furanyl
125		NH2	F	Cl	cyclobutyl	isobutyl	2,5-furanyl
126		NH2	F	Cl	cyclopropyl	isobutyl	2,5-furanyl
127		NH2	F	Cl	Phenyl	isobutyl	2,5-furanyl
128		NH2	F	SMe	Et	isobutyl	2,5-furanyl
129		NH2	F	SMe	Cl	isobutyl	2,5-furanyl
130		NH2	F	SMe	Br	isobutyl	2,5-furanyl
131		NH2	F	SMe	Me	isobutyl	2,5-furanyl
132		NH2	F	SMe	Pr	isobutyl	2,5-furanyl
133		NH2	F	SMe	i-Pr	isobutyl	2,5-furanyl
134		NH2	F	SMe	Bu	Isobutyl	2,5-furanyl
135		NH2	F	SMe	i-Bu	isobutyl	2,5-furanyl
136		NH2	F	SMe	OMe	isobutyl	2,5-furanyl
137		NH2	F	SMe	OEt	isobutyl	2,5-furanyl
138		NH2	F	SMe	SMe	isobutyl	2,5-furanyl
139		NH2	F	SMe	SEt	isobutyl	2,5-furanyl
140		NH2	F	SMe	NEt2	isobutyl	2,5-furanyl
141		NH2	F	SMe	NMe2	isobutyl	2,5-furanyl
142		NH2	F	SMe	I	isobutyl	2,5-furanyl
143		NH2	F	SMe	m-OMePhenyl	isobutyl	2,5-furanyl
144		NH2	F	SMe	o-OMePhenyl	isobutyl	2,5-furanyl
145		NH2	F	SMe	p-F Phenyl	isobutyl	2,5-furanyl

146		NH2	F	SMe	o-F Phenyl	isobutyl	2,5-furanyl
147		NH2	F	SMe	m-F Phenyl	isobutyl	2,5-furanyl
148		NH2	F	SMe	2-Furanyl	isobutyl	2,5-furanyl
149		NH2	F	SMe	2-thiophenyl	isobutyl	2,5-furanyl
150		NH2	F	SMe	2-Furanylmethyl	isobutyl	2,5-furanyl
151		NH2	F	SMe	2-Thiophenylmethyl	isobutyl	2,5-furanyl
152		NH2	F	SMe	CN	isobutyl	2,5-furanyl
153		NH2	F	SMe	m-Cl phenyl	isobutyl	2,5-furanyl
154		NH2	F	SMe	p-Cl phenyl	isobutyl	2,5-furanyl
155		NH2	F	SMe	o-Cl phenyl	isobutyl	2,5-furanyl
156		NH2	F	SMe	m-Br Phenyl	isobutyl	2,5-furanyl
157		NH2	F	SMe	p-Br Phenyl	isobutyl	2,5-furanyl
158		NH2	F	SMe	o-Br Phenyl	isobutyl	2,5-furanyl
159		NH2	F	SMe	CF3	isobutyl	2,5-furanyl
160		NH2	F	SMe	cyclopentyl	isobutyl	2,5-furanyl
161		NH2	F	SMe	cyclohexyl	isobutyl	2,5-furanyl
162		NH2	F	SMe	cyclobutyl	isobutyl	2,5-furanyl
163		NH2	F	SMe	Phenyl	isobutyl	2,5-furanyl
164		NH2	F	H	F	neopentyl	2,5-furanyl
165		NH2	F	H	Me	neopentyl	2,5-furanyl
166		NH2	F	H	Pr	neopentyl	2,5-furanyl
167		NH2	F	H	i-Pr	neopentyl	2,5-furanyl
168		NH2	F	H	Bu	neopentyl	2,5-furanyl
169		NH2	F	H	i-Bu	neopentyl	2,5-furanyl
170		NH2	F	H	OMe	neopentyl	2,5-furanyl
171		NH2	F	H	OEt	neopentyl	2,5-furanyl
172		NH2	F	H	SMe	neopentyl	2,5-furanyl
173		NH2	F	H	SEt	neopentyl	2,5-furanyl
174		NH2	F	H	NEt2	neopentyl	2,5-furanyl
175		NH2	F	H	NMe2	neopentyl	2,5-furanyl
176		NH2	F	H	I	neopentyl	2,5-furanyl
177		NH2	F	H	m-OMePhenyl	neopentyl	2,5-furanyl
178		NH2	F	H	o-OMePhenyl	neopentyl	2,5-furanyl
179		NH2	F	H	p-F Phenyl	neopentyl	2,5-furanyl

180		NH2	F	H	o-F Phenyl	neopentyl	2,5-furanyl
181		NH2	F	H	m-F Phenyl	neopentyl	2,5-furanyl
182		NH2	F	H	2-Furanyl	neopentyl	2,5-furanyl
183		NH2	F	H	2-thiophenyl	neopentyl	2,5-furanyl
184		NH2	F	H	2-Furanylmethyl	neopentyl	2,5-furanyl
185		NH2	F	H	2-Thiophenylmethyl	neopentyl	2,5-furanyl
186		NH2	F	H	CN	neopentyl	2,5-furanyl
187		NH2	F	H	m-Cl phenyl	neopentyl	2,5-furanyl
188		NH2	F	H	p-Cl phenyl	neopentyl	2,5-furanyl
189		NH2	F	H	o-Cl phenyl	neopentyl	2,5-furanyl
190		NH2	F	H	m-Br Phenyl	neopentyl	2,5-furanyl
191		NH2	F	H	p-Br Phenyl	neopentyl	2,5-furanyl
192		NH2	F	H	o-Br Phenyl	neopentyl	2,5-furanyl
193		NH2	F	H	CF3	neopentyl	2,5-furanyl
194		NH2	F	H	Phenyl	neopentyl	2,5-furanyl
195		NH2	F	H	cyclopentyl	neopentyl	2,5-furanyl
196		NH2	F	H	cyclohexyl	neopentyl	2,5-furanyl
197		NH2	F	H	cyclobutyl	neopentyl	2,5-furanyl
198		NH2	F	H	cyclopropyl	neopentyl	2,5-furanyl
199	12.61	NH2	F	H	H	cyclopropylmethyl	2,5-furanyl
200		NH2	F	H	F	cyclopropylmethyl	2,5-furanyl
201		NH2	F	H	Me	cyclopropylmethyl	2,5-furanyl
202		NH2	F	H	Pr	cyclopropylmethyl	2,5-furanyl
203		NH2	F	H	i-Pr	cyclopropylmethyl	2,5-furanyl
204		NH2	F	H	Bu	cyclopropylmethyl	2,5-furanyl
205		NH2	F	H	I-Bu	cyclopropylmethyl	2,5-furanyl
206		NH2	F	H	OMe	cyclopropylmethyl	2,5-furanyl
207		NH2	F	H	OEt	cyclopropylmethyl	2,5-furanyl
208		NH2	F	H	SMe	cyclopropylmethyl	2,5-furanyl
209		NH2	F	H	SEt	cyclopropylmethyl	2,5-furanyl
210		NH2	F	H	NEt2	cyclopropylmethyl	2,5-furanyl
211		NH2	F	H	NMe2	cyclopropylmethyl	2,5-furanyl
212		NH2	F	H	I	cyclopropylmethyl	2,5-furanyl
213		NH2	F	H	m-OMePhenyl	cyclopropylmethyl	2,5-furanyl

214		NH2	F	H	o-OMePhenyl	cyclopropylmethyl	2,5-furanyl
215		NH2	F	H	p-F Phenyl	cyclopropylmethyl	2,5-furanyl
216		NH2	F	H	o-F Phenyl	cyclopropylmethyl	2,5-furanyl
217		NH2	F	H	m-F Phenyl	cyclopropylmethyl	2,5-furanyl
218		NH2	F	H	2-Furanyl	cyclopropylmethyl	2,5-furanyl
219		NH2	F	H	2-thiophenyl	cyclopropylmethyl	2,5-furanyl
220		NH2	F	H	2-Furanylmethyl	cyclopropylmethyl	2,5-furanyl
221		NH2	F	H	2-Thiophenylmethyl	cyclopropylmethyl	2,5-furanyl
222		NH2	F	H	CN	cyclopropylmethyl	2,5-furanyl
223		NH2	F	H	m-Cl phenyl	cyclopropylmethyl	2,5-furanyl
224		NH2	F	H	p-Cl phenyl	cyclopropylmethyl	2,5-furanyl
225		NH2	F	H	o-Cl phenyl	cyclopropylmethyl	2,5-furanyl
226		NH2	F	H	m-Br Phenyl	cyclopropylmethyl	2,5-furanyl
227		NH2	F	H	p-Br Phenyl	cyclopropylmethyl	2,5-furanyl
228		NH2	F	H	o-Br Phenyl	cyclopropylmethyl	2,5-furanyl
229		NH2	F	H	CF3	cyclopropylmethyl	2,5-furanyl
230		NH2	F	H	Phenyl	cyclopropylmethyl	2,5-furanyl
231		NH2	F	H	cyclopentyl	neopentyl	2,5-furanyl
232		NH2	F	H	cyclohexyl	neopentyl	2,5-furanyl
233		NH2	F	H	cyclobutyl	neopentyl	2,5-furanyl
234		NH2	F	H	cyclopropyl	neopentyl	2,5-furanyl
235		NH2	F	H	cyclopentylmethyl	neopentyl	2,5-furanyl
236		NH2	F	H	cyclohexylmethyl	neopentyl	2,5-furanyl
237		NH2	F	H	cyclobutylmethyl	neopentyl	2,5-furanyl
238		NH2	F	H	cyclopropylmethyl	neopentyl	2,5-furanyl
239		NH2	F	H	F	cyclobutylmethyl	2,5-furanyl
240		NH2	F	H	Me	cyclobutylmethyl	2,5-furanyl
241		NH2	F	H	Pr	cyclobutylmethyl	2,5-furanyl
242		NH2	F	H	i-Pr	cyclobutylmethyl	2,5-furanyl
243		NH2	F	H	Bu	cyclobutylmethyl	2,5-furanyl
244		NH2	F	H	i-Bu	cyclobutylmethyl	2,5-furanyl
245		NH2	F	H	OMe	cyclobutylmethyl	2,5-furanyl
246		NH2	F	H	OEt	cyclobutylmethyl	2,5-furanyl
247		NH2	F	H	SMe	cyclobutylmethyl	2,5-furanyl

248		NH2	F	H	SEt	cyclobutylmethyl	2,5-furanyl
249		NH2	F	H	NEt2	cyclobutylmethyl	2,5-furanyl
250		NH2	F	H	NMe2	cyclobutylmethyl	2,5-furanyl
251		NH2	F	H	I	cyclobutylmethyl	2,5-furanyl
252		NH2	F	H	m-OMePhenyl	cyclobutylmethyl	2,5-furanyl
253		NH2	F	H	o-OMePhenyl	cyclobutylmethyl	2,5-furanyl
254		NH2	F	H	p-F Phenyl	cyclobutylmethyl	2,5-furanyl
255		NH2	F	H	o-F Phenyl	cyclobutylmethyl	2,5-furanyl
256		NH2	F	H	m-F Phenyl	cyclobutylmethyl	2,5-furanyl
257		NH2	F	H	2-Furanyl	cyclobutylmethyl	2,5-furanyl
258		NH2	F	H	2-thiophenyl	cyclobutylmethyl	2,5-furanyl
259		NH2	F	H	2-Furanylmethyl	cyclobutylmethyl	2,5-furanyl
260		NH2	F	H	2-Thiophenylmethyl	cyclobutylmethyl	2,5-furanyl
261		NH2	F	H	CN	cyclobutylmethyl	2,5-furanyl
262		NH2	F	H	m-Cl phenyl	cyclobutylmethyl	2,5-furanyl
263		NH2	F	H	p-Cl phenyl	cyclobutylmethyl	2,5-furanyl
264		NH2	F	H	o-Cl phenyl	cyclobutylmethyl	2,5-furanyl
265		NH2	F	H	m-Br Phenyl	cyclobutylmethyl	2,5-furanyl
266		NH2	F	H	p-Br Phenyl	cyclobutylmethyl	2,5-furanyl
267		NH2	F	H	o-Br Phenyl	cyclobutylmethyl	2,5-furanyl
268		NH2	F	H	CF3	cyclobutylmethyl	2,5-furanyl
269		NH2	F	H	Phenyl	cyclobutylmethyl	2,5-furanyl
270		NH2	F	F	F	isobutyl	2,5-furanyl
271	12.63	NH2	F	Cl	H	isobutyl	2,5-furanyl
272		NH2	F	F	Et	isobutyl	2,5-furanyl
273		NH2	F	Cl	Et	isobutyl	2,5-furanyl
274		NH2	F	H	Et	cyclopropylmethyl	2,5-furanyl
275		NH2	F	H	Et	cyclobutylmethyl	2,5-furanyl
276		NH2	F	Me	H	isobutyl	2,5-furanyl
277		NH2	F	Me	Me	isobutyl	2,5-furanyl
278		NH2	F	Me	Et	isobutyl	2,5-furanyl
279		NH2	F	F	Pr	isobutyl	2,5-furanyl
280		NH2	F	Me	Pr	isobutyl	2,5-furanyl
281		NH2	F	Cl	Pr	isobutyl	2,5-furanyl

282		NH2	F	H	H	isobutyl	methoxymethyl
283		NH2	F	H	H	cyclopropylmethyl	methoxymethyl
284		NH2	F	H	Et	isobutyl	methoxymethyl
285		NH2	F	H	Et	cyclopropylmethyl	methoxymethyl
286		OH	F	H	F	isobutyl	2,5-furanyl
287		OH	F	H	Me	isobutyl	2,5-furanyl
288		OH	F	H	Pr	isobutyl	2,5-furanyl
289		OH	F	H	i-Pr	isobutyl	2,5-furanyl
290		OH	F	H	Bu	isobutyl	2,5-furanyl
291		OH	F	H	i-Bu	isobutyl	2,5-furanyl
292		OH	F	H	OMe	isobutyl	2,5-furanyl
293		OH	F	H	OEt	isobutyl	2,5-furanyl
294		OH	F	H	SMe	isobutyl	2,5-furanyl
295		OH	F	H	SEt	isobutyl	2,5-furanyl
296		OH	F	H	NEt2	isobutyl	2,5-furanyl
297		OH	F	H	NMe2	isobutyl	2,5-furanyl
298		OH	F	H	I	isobutyl	2,5-furanyl
299		OH	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
300		OH	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
301		OH	F	H	p-F Phenyl	isobutyl	2,5-furanyl
302		OH	F	H	o-F Phenyl	isobutyl	2,5-furanyl
303		OH	F	H	m-F Phenyl	isobutyl	2,5-furanyl
304		OH	F	H	2-Furanyl	isobutyl	2,5-furanyl
305		OH	F	H	2-thiophenyl	isobutyl	2,5-furanyl
306		OH	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
307		OH	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
308		OH	F	H	CN	isobutyl	2,5-furanyl
309		OH	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
310		OH	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
311		OH	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
312		OH	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
313		OH	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
314		OH	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
315		OH	F	H	CF3	isobutyl	2,5-furanyl

316		OH	F	H	Phenyl	isobutyl	2,5-furanyl
317		OH	F	H	Cl	isobutyl	2,5-furanyl
318		OH	F	H	Br	isobutyl	2,5-furanyl
319		OH	F	H	Et	isobutyl	2,5-furanyl
320		NH2	F	F	Cl	isobutyl	2,5-furanyl
321		NH2	F	F	Br	isobutyl	2,5-furanyl
322	13.51	NH2	OH	H	H	isobutyl	2,5-furanyl
323		NH2	OH	H	F	isobutyl	2,5-furanyl
324		NH2	OH	H	Me	isobutyl	2,5-furanyl
325		NH2	OH	H	Pr	isobutyl	2,5-furanyl
326		NH2	OH	H	i-Pr	isobutyl	2,5-furanyl
327		NH2	OH	H	Bu	isobutyl	2,5-furanyl
328		NH2	OH	H	i-Bu	isobutyl	2,5-furanyl
329		NH2	OH	H	OMe	isobutyl	2,5-furanyl
330		NH2	OH	H	OEt	isobutyl	2,5-furanyl
331		NH2	OH	H	SMe	isobutyl	2,5-furanyl
332		NH2	OH	H	SEt	isobutyl	2,5-furanyl
333		NH2	OH	H	NEt2	isobutyl	2,5-furanyl
334		NH2	OH	H	NMe2	isobutyl	2,5-furanyl
335		NH2	OH	H	I	isobutyl	2,5-furanyl
336		NH2	OH	H	m-OMePhenyl	isobutyl	2,5-furanyl
337		NH2	OH	H	o-OMePhenyl	isobutyl	2,5-furanyl
338		NH2	OH	H	p-F Phenyl	isobutyl	2,5-furanyl
339		NH2	OH	H	o-F Phenyl	isobutyl	2,5-furanyl
340		NH2	OH	H	m-F Phenyl	isobutyl	2,5-furanyl
341		NH2	OH	H	2-Furanyl	isobutyl	2,5-furanyl
342		NH2	OH	H	2-thiophenyl	isobutyl	2,5-furanyl
343		NH2	OH	H	2-Furanylmethyl	isobutyl	2,5-furanyl
344		NH2	OH	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
345		NH2	OH	H	CN	isobutyl	2,5-furanyl
346		NH2	OH	H	m-Cl phenyl	isobutyl	2,5-furanyl
347		NH2	OH	H	p-Cl phenyl	isobutyl	2,5-furanyl
348		NH2	OH	H	o-Cl phenyl	isobutyl	2,5-furanyl
349		NH2	OH	H	m-Br Phenyl	isobutyl	2,5-furanyl

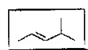
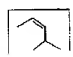
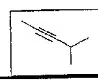
350		NH2	OH	H	p-Br Phenyl	isobutyl	2,5-furanyl
351		NH2	OH	H	o-Br Phenyl	isobutyl	2,5-furanyl
352		NH2	OH	H	CF3	isobutyl	2,5-furanyl
353		NH2	OH	H	Phenyl	isobutyl	2,5-furanyl
354	12.55	NH2	OMe	H	H	isobutyl	2,5-furanyl
355		NH2	OMe	H	F	isobutyl	2,5-furanyl
356		NH2	OMe	H	Me	isobutyl	2,5-furanyl
357		NH2	OMe	H	Pr	isobutyl	2,5-furanyl
358		NH2	OMe	H	i-Pr	isobutyl	2,5-furanyl
359		NH2	OMe	H	Bu	isobutyl	2,5-furanyl
360		NH2	OMe	H	i-Bu	isobutyl	2,5-furanyl
361		NH2	OMe	H	OMe	isobutyl	2,5-furanyl
362		NH2	OMe	H	OEt	isobutyl	2,5-furanyl
363		NH2	OMe	H	SMe	isobutyl	2,5-furanyl
364		NH2	OMe	H	SEt	isobutyl	2,5-furanyl
365		NH2	OMe	H	NEt2	isobutyl	2,5-furanyl
366		NH2	OMe	H	NMe2	isobutyl	2,5-furanyl
367		NH2	OMe	H	I	isobutyl	2,5-furanyl
368		NH2	OMe	H	m-OMePhenyl	isobutyl	2,5-furanyl
369		NH2	OMe	H	o-OMePhenyl	isobutyl	2,5-furanyl
370		NH2	OMe	H	p-F Phenyl	isobutyl	2,5-furanyl
371		NH2	OMe	H	o-F Phenyl	isobutyl	2,5-furanyl
372		NH2	OMe	H	m-F Phenyl	isobutyl	2,5-furanyl
373		NH2	OMe	H	2-Furanyl	isobutyl	2,5-furanyl
374		NH2	OMe	H	2-thiophenyl	isobutyl	2,5-furanyl
375		NH2	OMe	H	2-Furanylmethyl	isobutyl	2,5-furanyl
376		NH2	OMe	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
377		NH2	OMe	H	CN	isobutyl	2,5-furanyl
378		NH2	OMe	H	m-Cl phenyl	isobutyl	2,5-furanyl
379		NH2	OMe	H	p-Cl phenyl	isobutyl	2,5-furanyl
380		NH2	OMe	H	o-Cl phenyl	isobutyl	2,5-furanyl
381		NH2	OMe	H	m-Br Phenyl	isobutyl	2,5-furanyl
382		NH2	OMe	H	p-Br Phenyl	isobutyl	2,5-furanyl
383		NH2	OMe	H	o-Br Phenyl	isobutyl	2,5-furanyl

384		NH2	OMe	H	CF3	isobutyl	2,5-furanyl
385		NH2	OMe	H	Phenyl	isobutyl	2,5-furanyl
386		NH2	Cl	H	F	isobutyl	2,5-furanyl
387		NH2	Cl	H	Me	isobutyl	2,5-furanyl
388		NH2	Cl	H	Pr	isobutyl	2,5-furanyl
389		NH2	Cl	H	i-Pr	isobutyl	2,5-furanyl
390		NH2	Cl	H	Bu	isobutyl	2,5-furanyl
391		NH2	Cl	H	i-Bu	isobutyl	2,5-furanyl
392		NH2	Cl	H	OMe	isobutyl	2,5-furanyl
393		NH2	Cl	H	OEt	isobutyl	2,5-furanyl
394		NH2	Cl	H	SMe	isobutyl	2,5-furanyl
395		NH2	Cl	H	SEt	isobutyl	2,5-furanyl
396		NH2	Cl	H	NEt2	isobutyl	2,5-furanyl
397		NH2	Cl	H	NMe2	isobutyl	2,5-furanyl
398		NH2	Cl	H	I	isobutyl	2,5-furanyl
399		NH2	Cl	H	m-OMePhenyl	isobutyl	2,5-furanyl
400		NH2	Cl	H	o-OMePhenyl	isobutyl	2,5-furanyl
401		NH2	Cl	H	p-F Phenyl	isobutyl	2,5-furanyl
402		NH2	Cl	H	o-F Phenyl	isobutyl	2,5-furanyl
403		NH2	Cl	H	m-F Phenyl	isobutyl	2,5-furanyl
404		NH2	Cl	H	2-Furanyl	isobutyl	2,5-furanyl
405		NH2	Cl	H	2-thiophenyl	isobutyl	2,5-furanyl
406		NH2	Cl	H	2-Furanylmethyl	isobutyl	2,5-furanyl
407		NH2	Cl	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
408		NH2	Cl	H	CN	isobutyl	2,5-furanyl
409		NH2	Cl	H	m-Cl phenyl	isobutyl	2,5-furanyl
410		NH2	Cl	H	p-Cl phenyl	isobutyl	2,5-furanyl
411		NH2	Cl	H	o-Cl phenyl	isobutyl	2,5-furanyl
412		NH2	Cl	H	m-Br Phenyl	isobutyl	2,5-furanyl
413		NH2	Cl	H	p-Br Phenyl	isobutyl	2,5-furanyl
414		NH2	Cl	H	o-Br Phenyl	isobutyl	2,5-furanyl
415		NH2	Cl	H	CF3	isobutyl	2,5-furanyl
416		NH2	Cl	H	Phenyl	isobutyl	2,5-furanyl
417		NH2	Cl	H	Et	isobutyl	2,5-furanyl

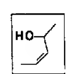
418		NH2	Cl	H	Br	isobutyl	2,5-furanyl
419	12.50	NH2	Cl	H	Cl	isobutyl	2,5-furanyl
420	12.49	NH2	Cl	H	H	isobutyl	2,5-furanyl
421	12.58	NH2	Br	Cl	Cl	isobutyl	2,5-furanyl
422		NH2	Br	H	Cl	isobutyl	2,5-furanyl
423	12.44	NH2	Br	H	H	isobutyl	2,5-furanyl
424	12.42	NH2	Br	H	Br	isobutyl	2,5-furanyl
425		NH2	Br	H	F	isobutyl	2,5-furanyl
426		NH2	Br	H	Me	isobutyl	2,5-furanyl
427		NH2	Br	H	Pr	isobutyl	2,5-furanyl
428		NH2	Br	H	i-Pr	isobutyl	2,5-furanyl
429		NH2	Br	H	Bu	isobutyl	2,5-furanyl
430		NH2	Br	H	i-Bu	isobutyl	2,5-furanyl
431		NH2	Br	H	OMe	isobutyl	2,5-furanyl
432		NH2	Br	H	OEt	isobutyl	2,5-furanyl
433		NH2	Br	H	SMe	isobutyl	2,5-furanyl
434		NH2	Br	H	SEt	isobutyl	2,5-furanyl
435		NH2	Br	H	NEt2	isobutyl	2,5-furanyl
436		NH2	Br	H	NMe2	isobutyl	2,5-furanyl
437		NH2	Br	H	I	isobutyl	2,5-furanyl
438		NH2	Br	H	m-OMePhenyl	isobutyl	2,5-furanyl
439		NH2	Br	H	o-OMePhenyl	isobutyl	2,5-furanyl
440		NH2	Br	H	p-F Phenyl	isobutyl	2,5-furanyl
441		NH2	Br	H	o-F Phenyl	isobutyl	2,5-furanyl
442		NH2	Br	H	m-F Phenyl	isobutyl	2,5-furanyl
443		NH2	Br	H	2-Furanyl	isobutyl	2,5-furanyl
444		NH2	Br	H	2-thiophenyl	isobutyl	2,5-furanyl
445		NH2	Br	H	2-Furanylmethyl	isobutyl	2,5-furanyl
446		NH2	Br	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
447		NH2	Br	H	CN	isobutyl	2,5-furanyl
448		NH2	Br	H	m-Cl phenyl	isobutyl	2,5-furanyl
449		NH2	Br	H	p-Cl phenyl	isobutyl	2,5-furanyl
450		NH2	Br	H	o-Cl phenyl	isobutyl	2,5-furanyl
451		NH2	Br	H	m-Br Phenyl	isobutyl	2,5-furanyl

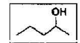
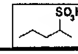
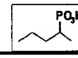
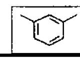
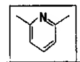
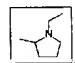
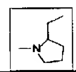
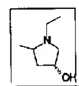
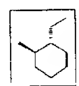
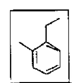
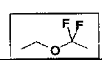
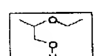
452		NH2	Br	H	p-Br Phenyl	isobutyl	2,5-furanyl
453		NH2	Br	H	o-Br Phenyl	isobutyl	2,5-furanyl
454		NH2	Br	H	CF3	isobutyl	2,5-furanyl
455		NH2	Br	H	Phenyl	isobutyl	2,5-furanyl
456		NH2	Br	H	Cl	isobutyl	2,5-furanyl
457		NH2	Br	H	Et	isobutyl	2,5-furanyl
458		NH2	Br	Cl	Cl	isobutyl	2,5-furanyl
459		NH2	Br	Cl	F	isobutyl	2,5-furanyl
460		NH2	Br	F	Cl	isobutyl	2,5-furanyl
461	12.65	Et	H	F	NH2	isobutyl	2,5-furanyl
462	13.1	H	H	H	H	H	2,5-furanyl
463	13.2	H	H	H	H	isobutyl	2,5-furanyl
464	13.6	H	CF3	H	H	H	2,5-furanyl
465	13.7	H	F	H	H	H	2,5-furanyl
466	13.8	H	Cl	Cl	H	H	2,5-furanyl
467	13.9	H	Cl	H	H	H	2,5-furanyl
468	13.10	H	Me	H	H	H	2,5-furanyl
469	13.11	H	t-Bu	H	H	H	2,5-furanyl
470	13.12	H	H	H	H	Ph	2,5-furanyl
471	13.13	H	H	H	H	2-CO2H-Phenyl	2,5-furanyl
472	13.14	H	NO2	H	H	H	2,5-furanyl
473	13.15	Me	Me	H	H	H	2,5-furanyl
474	13.16	H	Cl	H	H	isobutyl	2,5-furanyl
475	13.17	H	H	Cl	H	isobutyl	2,5-furanyl
476	13.18	H	C6H5CO	H	H	H	2,5-furanyl
477	13.19	amidino-methyl	H	H	H	2-ethylpentyl	2,5-furanyl
478	13.20	iso-butyloxy	H	H	H	isobutyl	2,5-furanyl
479	13.21	OH	H	H	H	isobutyl	2,5-furanyl
480	13.22	H	F	F	H	H	2,5-furanyl
481	13.23	H	CO2Me	H	H	H	2,5-furanyl
482	13.24	H	Me	Me	H	H	2,5-furanyl
483	13.25	F	H	H	H	neopentyl	2,5-furanyl

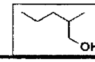
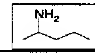
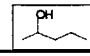
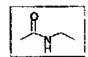
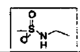
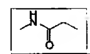
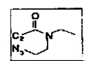
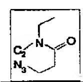
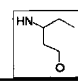
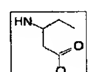
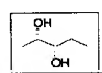
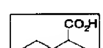
484	13.27	H	H	F	H	isobutyl	2,5-furanyl
485	13.28	H	F	H	H	isobutyl	2,5-furanyl
486		pyridyl	H	H	H	H	2,5-furanyl
487	13.32	Me	H	H	H	H	2,5-furanyl
488	13.33	H	Cl	H	H	isopropyl	2,5-furanyl
489	13.35	H	Br	H	H	H	2,5-furanyl
490	13.36	H	Br	H	H	isobutyl	2,5-furanyl
491	13.37	H	H	Br	H	isobutyl	2,5-furanyl
492	13.38	Cl	H	Cl	H	H	2,5-furanyl
493	13.39	Cl	H	Cl	H	isobutyl	2,5-furanyl
494		H	H	H	H	Ph	2,5-furanyl
495	13.40	H	Cl	H	H	Ph	2,5-furanyl
496	13.41	H	H	Cl	H	Ph	2,5-furanyl
497	13.42	Br	H	Br	H	H	2,5-furanyl
498	13.43	Br	H	Br	H	isobutyl	2,5-furanyl
499	13.44	H	Cl	Cl	H	isobutyl	2,5-furanyl
500	13.45	H	Cl	Cl	H	cyclopropylmethyl	2,5-furanyl
501	13.46	H	Cl	F	H	H	2,5-furanyl
502	13.47	Ph	H	CF3	H	H	2,5-furanyl
503	13.48	Br	H	CF3	H	H	2,5-furanyl
504	13.49	H	Cl	F	H	cyclopropylmethyl	2,5-furanyl
505	13.50	H	Cl	F	H	isobutyl	2,5-furanyl
506	13.53	Me	Me	Br	H	isobutyl	2,5-furanyl
507	13.54	Me	H	H	H	isobutyl	2,5-furanyl
508		Me	H	H	H	neopentyl	2,5-furanyl
509		H	H	Cl	Br	isobutyl	2,5-furanyl
510		H	H	Cl	Br	isobutyl	2,5-furanyl
511		H	H	Cl	OH	isobutyl	2,5-furanyl
512		H	H	Cl	OMe	isobutyl	2,5-furanyl
513		H	H	Cl	CN	isobutyl	2,5-furanyl
514		H	H	Cl	CO2H	isobutyl	2,5-furanyl
515		H	H	Cl	CO2Me	isobutyl	2,5-furanyl
516		H	H	Cl	CONH2	isobutyl	2,5-furanyl
517		H	H	Cl	NHCONH2	isobutyl	2,5-furanyl

518		H	H	Cl	Me	isobutyl	2,5-furanyl
519		H	H	Cl	Et	isobutyl	2,5-furanyl
520		H	H	Cl	n-Pr	isobutyl	2,5-furanyl
521		H	H	Cl	l-Pr	isobutyl	2,5-furanyl
522		H	H	Cl	n-Bu	isobutyl	2,5-furanyl
523		H	H	Cl	i-butyl	isobutyl	2,5-furanyl
524		H	H	Cl	n-pentyl	isobutyl	2,5-furanyl
525		H	H	Cl	i-pentyl	isobutyl	2,5-furanyl
526		H	H	Cl	neo pentyl	isobutyl	2,5-furanyl
527		H	H	Cl	2-chloroethyl	isobutyl	2,5-furanyl
528		H	H	Cl	2-bromoethyl	isobutyl	2,5-furanyl
529		H	H	Cl	2-hydroxyethyl	isobutyl	2,5-furanyl
530		H	H	Cl	2-carboxyethyl	isobutyl	2,5-furanyl
531		H	H	Cl	2-carboxyamidoethyl	isobutyl	2,5-furanyl
532		H	H	Cl	3-carboxypropyl	isobutyl	2,5-furanyl
533		H	H	Cl	3-carboxyamidopropyl	isobutyl	2,5-furanyl
534		H	H	Cl		isobutyl	2,5-furanyl
535		H	H	Cl		isobutyl	2,5-furanyl
536		H	H	Cl		isobutyl	2,5-furanyl
537		H	H	Cl	Cyclopentyl	isobutyl	2,5-furanyl
538		H	H	Cl	Cyclopentylmethyl	isobutyl	2,5-furanyl
539		H	H	Cl	Cyclopentylethyl	isobutyl	2,5-furanyl
540		H	H	Cl	Phenyl	isobutyl	2,5-furanyl
541		H	H	Cl	benzyl	isobutyl	2,5-furanyl
542		H	H	Cl	phenethyl	isobutyl	2,5-furanyl
543		H	H	Cl	m-chlorophenyl	isobutyl	2,5-furanyl
544		H	H	Cl	p-chlorophenyl	isobutyl	2,5-furanyl
545		H	H	Cl	m-bromophenyl	isobutyl	2,5-furanyl

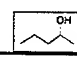
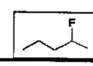
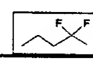
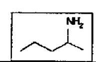
546		H	H	Cl	p-bromophenyl	isobutyl	2,5-furanyl
547		H	H	Cl	m-hydroxyphenyl	isobutyl	2,5-furanyl
548		H	H	Cl	p-hydroxyphenyl	isobutyl	2,5-furanyl
549		H	H	Cl	m-carboxyphenyl	isobutyl	2,5-furanyl
550		H	H	Cl	p-carboxyphenyl	isobutyl	2,5-furanyl
551		H	H	Cl	m-carboxyamidophenyl	isobutyl	2,5-furanyl
552		H	H	Cl	p-carboxyamidophenyl	isobutyl	2,5-furanyl
553		H	H	Cl	N-pyrrolidinyl	isobutyl	2,5-furanyl
554		H	H	Cl	N-thiomorpholinyl	isobutyl	2,5-furanyl
555		H	H	Cl	N-imidazolyl	isobutyl	2,5-furanyl
556		H	H	Cl	N-piperdinylmethyl	isobutyl	2,5-furanyl
557		H	H	Cl	N-piperazinylmethyl	isobutyl	2,5-furanyl
558		H	H	Cl	N-morpholinylmethyl	isobutyl	2,5-furanyl
559		H	H	Cl	N-pyrrolidinemythyl	isobutyl	2,5-furanyl
560		H	H	Cl	N-piperdinylethyl	isobutyl	2,5-furanyl
561		H	H	Cl	N-piperazinylethyl	isobutyl	2,5-furanyl
562		H	H	Cl	N-morpholinylethyl	isobutyl	2,5-furanyl
563		H	H	Cl	4-imdazolylethyl	isobutyl	2,5-furanyl
564		H	H	Cl	4-oxazolylethyl	isobutyl	2,5-furanyl
565		H	H	Cl	4-thiazolylethyl	isobutyl	2,5-furanyl
566		H	H	Cl	4-pyrimidylethyl	isobutyl	2,5-furanyl
567		H	H	Cl	5-pyrimidylethyl	isobutyl	2,5-furanyl
568		F	H	Cl	H	isobutyl	2,5-furanyl
569		Me	H	Cl	H	isobutyl	2,5-furanyl
570		Et	H	Cl	H	isobutyl	2,5-furanyl
571		n-Pr	H	Cl	H	isobutyl	2,5-furanyl
572		i-Pr	H	Cl	H	isobutyl	2,5-furanyl
573		acetyl	H	Cl	H	isobutyl	2,5-furanyl
574		carboxy	H	Cl	H	isobutyl	2,5-furanyl
575		carboxy-amido	H	Cl	H	isobutyl	2,5-furanyl
576		SH	H	Cl	H	isobutyl	2,5-furanyl

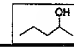
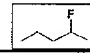
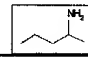
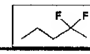
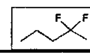
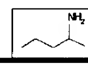
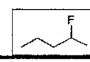
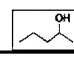
577		-NHNH2	H	Cl	H	isobutyl	2,5-furanyl
578		-NHOH	H	Cl	H	isobutyl	2,5-furanyl
579		H	Et	Cl	H	isobutyl	2,5-furanyl
580		H	CN	Cl	H	isobutyl	2,5-furanyl
581		H	CO2H	Cl	H	isobutyl	2,5-furanyl
582		H	CO2NH2	Cl	H	isobutyl	2,5-furanyl
583		H	H	Me	H	isobutyl	2,5-furanyl
584		H	H	acetenyl	H	isobutyl	2,5-furanyl
585		H	H	ethynyl	H	isobutyl	2,5-furanyl
586		H	H	ethyl	H	isobutyl	2,5-furanyl
587		H	H	NO2	H	isobutyl	2,5-furanyl
588		H	H	NH2	H	isobutyl	2,5-furanyl
589		H	H	CN	H	isobutyl	2,5-furanyl
590		H	H	SMe	H	isobutyl	2,5-furanyl
591		H	H	OMe	H	isobutyl	2,5-furanyl
592		H	H	phenyl	H	isobutyl	2,5-furanyl
593		H	H	Cl	H	m-OHPh	2,5-furanyl
594		H	H	Cl	H	p-OHPh	2,5-furanyl
595		H	H	Cl	H	m-CO2HPh	2,5-furanyl
596		H	H	Cl	H	p-CO2HPh	2,5-furanyl
597		H	H	Cl	H	m-CONH2Ph	2,5-furanyl
598		H	H	Cl	H	p-CO2HPh	2,5-furanyl
599		H	H	Cl	H	m-ClPh	2,5-furanyl
600		H	H	Cl	H	p-ClPh	2,5-furanyl
601		H	H	Cl	H	COCH2CH3	2,5-furanyl
602		H	H	Cl	H	COPh	2,5-furanyl
603		H	H	Cl	H	SO2CH3	2,5-furanyl
604		H	H	Cl	H	SO2Ph	2,5-furanyl
605		H	H	Cl	H	isobutyl	
606		H	H	Cl	H	isobutyl	

607		H	H	Cl	H	isobutyl	
608		H	H	Cl	H	isobutyl	
609		H	H	Cl	H	isobutyl	
610		H	H	Cl	H	isobutyl	
611		H	H	Cl	H	isobutyl	
612		H	H	Cl	H	isobutyl	
613		H	H	Cl	H	isobutyl	
614		H	H	Cl	H	isobutyl	
615		H	H	Cl	H	isobutyl	
616		H	H	Cl	H	isobutyl	
617		H	H	Cl	H	isobutyl	
618		H	H	Cl	H	isobutyl	

619		H	H	Cl	H	isobutyl	
620		H	H	Cl	H	isobutyl	
621		H	H	Cl	H	isobutyl	
622		H	H	Cl	H	isobutyl	
623		H	H	Cl	H	isobutyl	
624		H	H	Cl	H	isobutyl	
625		H	H	Cl	H	isobutyl	
626		H	H	Cl	H	isobutyl	
627		H	H	Cl	H	isobutyl	
628		H	H	Cl	H	isobutyl	
629		H	H	Cl	H	isobutyl	
630		H	H	Cl	H	isobutyl	
631		H	H	Cl	H	isobutyl	

632	13.63	H	Cl	Me	Me	isobutyl	2,5-furanyl
633	13.60	Me	Me	Cl	H	isobutyl	2,5-furanyl
634	13.58	H	H	Cl	H	cyclopropylmethyl	2,5-furanyl
635		Me	Me	H	H	isobutyl	2,5-furanyl
636	13.56	H	H	Cl	H	neopentyl	2,5-furanyl
637		Cl	H	Cl	H	neopentyl	2,5-furanyl
638		H	F	H	Et	isobutyl	2,5-furanyl
639		H	F	SMe	Et	isobutyl	2,5-furanyl
640		H	F	Cl	Et	isobutyl	2,5-furanyl
641		H	F	Br	Et	isobutyl	2,5-furanyl
642		H	F	Cl	Br	isobutyl	2,5-furanyl
643		H	H	Cl	H	neopentyl	2,5-furanyl
644		H	F	F	H	H	2,5-furanyl
645		NH2	F	H	2,6-difluorophenyl	isobutyl	methoxymethyl
646		NH2	F	H	Br	isobutyl	methoxymethyl
647		NH2	F	H	H	isobutyl	methoxymethyl
648		NH2	F	H	Et	isobutyl	methoxymethyl
649		NH2	F	H	Cl	isobutyl	methoxymethyl
650		NH2	F	H	Me	isobutyl	methoxymethyl
651		NH2	F	H	Pr	isobutyl	methoxymethyl
652		NH2	F	H	i-Pr	isobutyl	methoxymethyl
653		NH2	F	H	Bu	isobutyl	methoxymethyl
654		NH2	F	H	i-Bu	isobutyl	methoxymethyl
655		NH2	F	H	OMe	isobutyl	methoxymethyl
656		NH2	F	H	OEt	isobutyl	methoxymethyl
657		NH2	F	H	SMe	isobutyl	methoxymethyl
658		NH2	F	H	SEt	isobutyl	methoxymethyl
659		NH2	F	H	NEt2	isobutyl	methoxymethyl
660		NH2	F	H	NMe2	isobutyl	methoxymethyl
661		NH2	F	H	I	isobutyl	methoxymethyl
662		NH2	F	H	m-OMePhenyl	isobutyl	methoxymethyl
663		NH2	F	H	o-OMePhenyl	isobutyl	methoxymethyl
664		NH2	F	H	p-F Phenyl	isobutyl	methoxymethyl
665		NH2	F	H	o-F Phenyl	isobutyl	methoxymethyl

666		NH2	F	H	m-F Phenyl	isobutyl	methoxymethyl
667		NH2	F	H	2-Furanyl	isobutyl	methoxymethyl
668		NH2	F	H	2-thiophenyl	isobutyl	methoxymethyl
669		NH2	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
670		NH2	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
671		NH2	F	H	CN	isobutyl	methoxymethyl
672		NH2	F	H	m-Cl phenyl	isobutyl	methoxymethyl
673		NH2	F	H	p-Cl phenyl	isobutyl	methoxymethyl
674		NH2	F	H	o-Cl phenyl	isobutyl	methoxymethyl
675		NH2	F	H	m-Br Phenyl	isobutyl	methoxymethyl
676		NH2	F	H	p-Br Phenyl	isobutyl	methoxymethyl
677		NH2	F	H	o-Br Phenyl	isobutyl	methoxymethyl
678		NH2	F	H	CF3	isobutyl	methoxymethyl
679		NH2	F	H	cyclopentyl	isobutyl	methoxymethyl
680		NH2	F	H	cyclohexyl	isobutyl	methoxymethyl
681		NH2	F	H	cyclobutyl	isobutyl	methoxymethyl
682		NH2	F	H	cyclopropyl	isobutyl	methoxymethyl
683		NH2	F	H	Phenyl	isobutyl	methoxymethyl
684		NH2	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
685		NH2	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
686		NH2	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
687		NH2	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
688		NH2	F	H	Et	neopentyl	2,5-furanyl
689		NH2	F	H	Et	Ph	2,5-furanyl
690		NH2	F	H	Et	isobutyl	
691		NH2	F	H	Et	isobutyl	
692		NH2	F	H	Et	isobutyl	
693		NH2	F	H	Et	isobutyl	

694		NH2	F	H	Et	Isobutyl	CONHCH2
695		NH2	F	H	Et	isobutyl	NHCOCH2
696		NH2	F	Cl	Et	isobutyl	
697		NH2	F	Cl	Et	isobutyl	
698		NH2	F	Cl	Et	isobutyl	
699		NH2	F	Cl	Et	isobutyl	
700		NH2	F	Cl	Et	isobutyl	CONHCH2
701		NH2	F	Cl	Et	isobutyl	NHCOCH2
702	13.4	H	$-(CH_2)_3-$		H	isobutyl	2,5-furanyl
703	13.3	H	$-(CH_2)_3-$		H	H	2,5-furanyl
704		H	H		$-(CH_2)_3-$	1,7-cyclohexyl	2,5-furanyl
705		Me	Me	Cl	Et	cyclopropylmethyl	2,5-furanyl
706		Me	Me	Cl	Cl	cyclopropylmethyl	2,5-furanyl
707		Me	Me	Cl	H	cyclopropylmethyl	methoxymethyl
708		Me	Me	Cl	H	cyclopropylmethyl	
709		Me	Me	Cl	H	cyclopropylmethyl	
710		Me	Me	Cl	H	cyclopropylmethyl	
711		Me	Me	Cl	H	cyclopropylmethyl	
712		Me	Me	Cl	H	cyclopropylmethyl	NHCOCH2
713		Me	Me	Cl	H	cyclopropylmethyl	CONHCH2
714		Me	Me	Cl	H	Ph	2,5-furanyl
715		Me	Me	Cl	H	cyclobutylmethyl	2,5-furanyl
716		Me	Me	Cl	F	cyclopropylmethyl	2,5-furanyl

717		Me	Me	Cl	Pr	cyclopropylmethyl	2,5-furanyl
718		Me	Me	Cl	Bu	cyclopropylmethyl	2,5-furanyl
719		Me	Me	Cl	OMe	cyclopropylmethyl	2,5-furanyl
720		Me	Me	Cl	OEt	cyclopropylmethyl	2,5-furanyl
721		Me	Me	Cl	I-Pr	cyclopropylmethyl	2,5-furanyl
722		Me	Me	SMe	H	cyclopropylmethyl	2,5-furanyl
723		Me	Me	F	H	cyclopropylmethyl	2,5-furanyl
724		Me	Me	Me	H	cyclopropylmethyl	2,5-furanyl
725		Cl	Cl	Cl	H	cyclopropylmethyl	2,5-furanyl
726		Me	Cl	Cl	H	cyclopropylmethyl	2,5-furanyl
727		Cl	Me	Cl	H	cyclopropylmethyl	2,5-furanyl
728		Cl	Cl	Me	H	cyclopropylmethyl	2,5-furanyl
729	12.7	NH2	H	H	H	isobutyl	2,5-furanyl
730	12.41	NH2	H	H	H	3-thienylmethyl	2,5-furanyl
731	12.43	NH2	H	H	H	1-hydroxypropyl-3-yl	2,5-furanyl
732	13.34	H	F	F	H	isobutyl	2,5-furanyl
733	13.55	H	H	H	Me	neopentyl	2,5-furanyl
734	13.57	H	Cl	H	H	cyclopropylmethyl	2,5-furanyl
735	13.61	Me	Me	Cl	H	cyclopropylmethyl	2,5-furanyl
736	13.62	H	H	Me	Me	isobutyl	2,5-furanyl
737	13.64	H	F	H	Br	isobutyl	2,5-furanyl
738	13.65	H	H	Cl	H	3-methoxyphenyl	2,5-furanyl
739	13.66	H	H	H	H	H	-C(O)NHCH2-
740		Me	F	H	Br	isobutyl	2,5-furanyl
741		Me	F	H	H	isobutyl	2,5-furanyl
742		Me	F	H	Et	isobutyl	2,5-furanyl
743		Me	F	H	Cl	isobutyl	2,5-furanyl
744		Me	F	H	Me	isobutyl	2,5-furanyl
745		Me	F	H	Pr	Isobutyl	2,5-furanyl
746		Me	F	H	i-Pr	Isobutyl	2,5-furanyl
747		Me	F	H	Bu	isobutyl	2,5-furanyl
748		Me	F	H	i-Bu	isobutyl	2,5-furanyl
749		Me	F	H	OMe	isobutyl	2,5-furanyl

750		Me	F	H	OEt	isobutyl	2,5-furanyl
751		Me	F	H	SMe	isobutyl	2,5-furanyl
752		Me	F	H	SEt	isobutyl	2,5-furanyl
753		Me	F	H	NEt2	isobutyl	2,5-furanyl
754		Me	F	H	NMe2	isobutyl	2,5-furanyl
755		Me	F	H	I	isobutyl	2,5-furanyl
756		Me	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
757		Me	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
758		Me	F	H	p-F Phenyl	isobutyl	2,5-furanyl
759		Me	F	H	o-F Phenyl	isobutyl	2,5-furanyl
760		Me	F	H	m-F Phenyl	isobutyl	2,5-furanyl
761		Me	F	H	2-Furanyl	isobutyl	2,5-furanyl
762		Me	F	H	2-thiophenyl	isobutyl	2,5-furanyl
763		Me	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
764		Me	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
765		Me	F	H	CN	isobutyl	2,5-furanyl
766		Me	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
767		Me	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
768		Me	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
769		Me	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
770		Me	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
771		Me	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
773		Me	F	H	CF3	isobutyl	2,5-furanyl
774		Me	F	H	cyclopentyl	isobutyl	2,5-furanyl
775		Me	F	H	cyclohexyl	isobutyl	2,5-furanyl
776		Me	F	H	cyclobutyl	isobutyl	2,5-furanyl
777		Me	F	H	cyclopropyl	isobutyl	2,5-furanyl
778		Me	F	H	Phenyl	isobutyl	2,5-furanyl
779		Me	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
780		Me	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
781		Me	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
782		Me	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
783		H	F	H	Br	isobutyl	2,5-furanyl
784		H	F	H	H	isobutyl	2,5-furanyl

785		H	F	H	Et	isobutyl	2,5-furanyl
786		H	F	H	Cl	isobutyl	2,5-furanyl
787		H	F	H	Me	isobutyl	2,5-furanyl
788		H	F	H	Pr	isobutyl	2,5-furanyl
789		H	F	H	I-Pr	isobutyl	2,5-furanyl
790		H	F	H	Bu	isobutyl	2,5-furanyl
791		H	F	H	I-Bu	isobutyl	2,5-furanyl
792		H	F	H	OMe	isobutyl	2,5-furanyl
793		H	F	H	OEt	isobutyl	2,5-furanyl
794		H	F	H	SMe	isobutyl	2,5-furanyl
795		H	F	H	SEt	isobutyl	2,5-furanyl
796		H	F	H	NEt2	isobutyl	2,5-furanyl
797		H	F	H	NMe2	isobutyl	2,5-furanyl
798		H	F	H	I	isobutyl	2,5-furanyl
799		H	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
800		H	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
801		H	F	H	p-F Phenyl	isobutyl	2,5-furanyl
802		H	F	H	o-F Phenyl	isobutyl	2,5-furanyl
803		H	F	H	m-F Phenyl	isobutyl	2,5-furanyl
804		H	F	H	2-Furanyl	isobutyl	2,5-furanyl
805		H	F	H	2-thiophenyl	isobutyl	2,5-furanyl
806		H	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
807		H	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
808		H	F	H	CN	isobutyl	2,5-furanyl
809		H	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
810		H	F	H	p-Cl phenyl	isobutyl	2,5-furanyl
811		H	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
812		H	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
813		H	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
814		H	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
815		H	F	H	CF3	isobutyl	2,5-furanyl
816		H	F	H	cyclopentyl	isobutyl	2,5-furanyl
817		H	F	H	cyclohexyl	isobutyl	2,5-furanyl
818		H	F	H	cyclobutyl	isobutyl	2,5-furanyl

819		H	F	H	cyclopropyl	isobutyl	2,5-furanyl
820		H	F	H	Phenyl	isobutyl	2,5-furanyl
821		H	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
822		H	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
823		H	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
824		H	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
825		Cl	F	H	Br	isobutyl	2,5-furanyl
826		Cl	F	H	H	isobutyl	2,5-furanyl
827		Cl	F	H	Et	isobutyl	2,5-furanyl
828		Cl	F	H	Cl	isobutyl	2,5-furanyl
829		Cl	F	H	Me	isobutyl	2,5-furanyl
830		Cl	F	H	Pr	isobutyl	2,5-furanyl
831		Cl	F	H	i-Pr	isobutyl	2,5-furanyl
832		Cl	F	H	Bu	isobutyl	2,5-furanyl
833		Cl	F	H	i-Bu	isobutyl	2,5-furanyl
834		Cl	F	H	OMe	isobutyl	2,5-furanyl
835		Cl	F	H	OEt	isobutyl	2,5-furanyl
836		Cl	F	H	SMe	isobutyl	2,5-furanyl
837		Cl	F	H	SEt	isobutyl	2,5-furanyl
838		Cl	F	H	NEt2	isobutyl	2,5-furanyl
839		Cl	F	H	NMe2	isobutyl	2,5-furanyl
840		Cl	F	H	I	isobutyl	2,5-furanyl
841		Cl	F	H	m-OMePhenyl	isobutyl	2,5-furanyl
842		Cl	F	H	o-OMePhenyl	isobutyl	2,5-furanyl
843		Cl	F	H	p-F Phenyl	isobutyl	2,5-furanyl
844		Cl	F	H	o-F Phenyl	isobutyl	2,5-furanyl
845		Cl	F	H	m-F Phenyl	isobutyl	2,5-furanyl
846		Cl	F	H	2-Furanyl	isobutyl	2,5-furanyl
847		Cl	F	H	2-thiophenyl	isobutyl	2,5-furanyl
848		Cl	F	H	2-Furanylmethyl	isobutyl	2,5-furanyl
849		Cl	F	H	2-Thiophenylmethyl	isobutyl	2,5-furanyl
850		Cl	F	H	CN	isobutyl	2,5-furanyl
851		Cl	F	H	m-Cl phenyl	isobutyl	2,5-furanyl
852		Cl	F	H	p-Cl phenyl	isobutyl	2,5-furanyl

853		Cl	F	H	o-Cl phenyl	isobutyl	2,5-furanyl
854		Cl	F	H	m-Br Phenyl	isobutyl	2,5-furanyl
855		Cl	F	H	p-Br Phenyl	isobutyl	2,5-furanyl
856		Cl	F	H	o-Br Phenyl	isobutyl	2,5-furanyl
857		Cl	F	H	CF3	isobutyl	2,5-furanyl
858		Cl	F	H	cyclopentyl	isobutyl	2,5-furanyl
859		Cl	F	H	cyclohexyl	isobutyl	2,5-furanyl
860		Cl	F	H	cyclobutyl	isobutyl	2,5-furanyl
861		Cl	F	H	cyclopropyl	isobutyl	2,5-furanyl
862		Cl	F	H	Phenyl	isobutyl	2,5-furanyl
863		Cl	F	H	cyclopentylmethyl	isobutyl	2,5-furanyl
864		Cl	F	H	cyclohexylmethyl	isobutyl	2,5-furanyl
865		Cl	F	H	cyclobutylmethyl	isobutyl	2,5-furanyl
866		Cl	F	H	cyclopropylmethyl	isobutyl	2,5-furanyl
867		Cl	F	H	Br	isobutyl	methoxymethyl
868		Cl	F	H	H	isobutyl	methoxymethyl
869		Cl	F	H	Et	isobutyl	methoxymethyl
870		Cl	F	H	Cl	isobutyl	methoxymethyl
871		Cl	F	H	Me	isobutyl	methoxymethyl
872		Cl	F	H	Pr	isobutyl	methoxymethyl
873		Cl	F	H	i-Pr	isobutyl	methoxymethyl
874		Cl	F	H	Bu	isobutyl	methoxymethyl
875		Cl	F	H	i-Bu	isobutyl	methoxymethyl
876		Cl	F	H	OMe	isobutyl	methoxymethyl
877		Cl	F	H	OEt	isobutyl	methoxymethyl
878		Cl	F	H	SMe	isobutyl	methoxymethyl
879		Cl	F	H	SEt	isobutyl	methoxymethyl
880		Cl	F	H	NEt2	isobutyl	methoxymethyl
881		Cl	F	H	NMe2	isobutyl	methoxymethyl
882		Cl	F	H	I	isobutyl	methoxymethyl
883		Cl	F	H	m-OMePhenyl	isobutyl	methoxymethyl
884		Cl	F	H	o-OMePhenyl	isobutyl	methoxymethyl
885		Cl	F	H	p-F Phenyl	isobutyl	methoxymethyl
886		Cl	F	H	o-F Phenyl	isobutyl	methoxymethyl

887		Cl	F	H	m-F Phenyl	isobutyl	methoxymethyl
888		Cl	F	H	2-Furanyl	isobutyl	methoxymethyl
889		Cl	F	H	2-thiophenyl	isobutyl	methoxymethyl
890		Cl	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
891		Cl	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
892		Cl	F	H	CN	isobutyl	methoxymethyl
893		Cl	F	H	m-Cl phenyl	isobutyl	methoxymethyl
894		Cl	F	H	p-Cl phenyl	isobutyl	methoxymethyl
895		Cl	F	H	o-Cl phenyl	isobutyl	methoxymethyl
896		Cl	F	H	m-Br Phenyl	isobutyl	methoxymethyl
897		Cl	F	H	p-Br Phenyl	isobutyl	methoxymethyl
898		Cl	F	H	o-Br Phenyl	isobutyl	methoxymethyl
899		Cl	F	H	CF3	isobutyl	methoxymethyl
900		Cl	F	H	cyclopentyl	isobutyl	methoxymethyl
901		Cl	F	H	cyclohexyl	isobutyl	methoxymethyl
902		Cl	F	H	cyclobutyl	isobutyl	methoxymethyl
903		Cl	F	H	cyclopropyl	isobutyl	methoxymethyl
904		Cl	F	H	Phenyl	isobutyl	methoxymethyl
905		Cl	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
906		Cl	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
907		Cl	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
908		Cl	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
909		H	F	H	Br	isobutyl	methoxymethyl
910		H	F	H	H	isobutyl	methoxymethyl
911		H	F	H	Et	isobutyl	methoxymethyl
912		H	F	H	Cl	isobutyl	methoxymethyl
913		H	F	H	Me	isobutyl	methoxymethyl
914		H	F	H	Pr	isobutyl	methoxymethyl
915		H	F	H	i-Pr	isobutyl	methoxymethyl
916		H	F	H	Bu	isobutyl	methoxymethyl
917		H	F	H	i-Bu	isobutyl	methoxymethyl
918		H	F	H	OMe	isobutyl	methoxymethyl
919		H	F	H	OEt	isobutyl	methoxymethyl
920		H	F	H	SMe	isobutyl	methoxymethyl

921		H	F	H	SEt	isobutyl	methoxymethyl
922		H	F	H	NEt2	isobutyl	methoxymethyl
923		H	F	H	NMe2	isobutyl	methoxymethyl
924		H	F	H	I	isobutyl	methoxymethyl
925		H	F	H	m-OMePhenyl	isobutyl	methoxymethyl
926		H	F	H	o-OMePhenyl	isobutyl	methoxymethyl
927		H	F	H	p-F Phenyl	isobutyl	methoxymethyl
928		H	F	H	o-F Phenyl	isobutyl	methoxymethyl
929		H	F	H	m-F Phenyl	isobutyl	methoxymethyl
930		H	F	H	2-Furanyl	isobutyl	methoxymethyl
931		H	F	H	2-thiophenyl	isobutyl	methoxymethyl
932		H	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
933		H	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
934		H	F	H	CN	isobutyl	methoxymethyl
935		H	F	H	m-Cl phenyl	isobutyl	methoxymethyl
936		H	F	H	p-Cl phenyl	isobutyl	methoxymethyl
937		H	F	H	o-Cl phenyl	isobutyl	methoxymethyl
938		H	F	H	m-Br Phenyl	isobutyl	methoxymethyl
939		H	F	H	p-Br Phenyl	isobutyl	methoxymethyl
940		H	F	H	o-Br Phenyl	isobutyl	methoxymethyl
941		H	F	H	CF3	isobutyl	methoxymethyl
942		H	F	H	cyclopentyl	isobutyl	methoxymethyl
943		H	F	H	cyclohexyl	isobutyl	methoxymethyl
944		H	F	H	cyclobutyl	isobutyl	methoxymethyl
945		H	F	H	cyclopropyl	isobutyl	methoxymethyl
946		H	F	H	Phenyl	isobutyl	methoxymethyl
947		H	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
948		H	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
949		H	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
950		H	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
951		Me	F	H	Br	isobutyl	methoxymethyl
952		Me	F	H	H	isobutyl	methoxymethyl
953		Me	F	H	Et	isobutyl	methoxymethyl
954		Me	F	H	Cl	isobutyl	methoxymethyl

955		Me	F	H	Me	isobutyl	methoxymethyl
956		Me	F	H	Pr	isobutyl	methoxymethyl
957		Me	F	H	i-Pr	isobutyl	methoxymethyl
958		Me	F	H	Bu	isobutyl	methoxymethyl
959		Me	F	H	i-Bu	isobutyl	methoxymethyl
960		Me	F	H	OMe	isobutyl	methoxymethyl
961		Me	F	H	OEt	isobutyl	methoxymethyl
962		Me	F	H	SMe	isobutyl	methoxymethyl
963		Me	F	H	SEt	isobutyl	methoxymethyl
964		Me	F	H	NEt2	isobutyl	methoxymethyl
965		Me	F	H	NMe2	isobutyl	methoxymethyl
966		Me	F	H	I	isobutyl	methoxymethyl
967		Me	F	H	m-OMePhenyl	isobutyl	methoxymethyl
968		Me	F	H	o-OMePhenyl	isobutyl	methoxymethyl
969		Me	F	H	p-F Phenyl	isobutyl	methoxymethyl
970		Me	F	H	o-F Phenyl	isobutyl	methoxymethyl
971		Me	F	H	m-F Phenyl	isobutyl	methoxymethyl
972		Me	F	H	2-Furanyl	isobutyl	methoxymethyl
973		Me	F	H	2-thiophenyl	isobutyl	methoxymethyl
974		Me	F	H	2-Furanylmethyl	isobutyl	methoxymethyl
975		Me	F	H	2-Thiophenylmethyl	isobutyl	methoxymethyl
976		Me	F	H	CN	isobutyl	methoxymethyl
977		Me	F	H	m-Cl phenyl	isobutyl	methoxymethyl
978		Me	F	H	p-Cl phenyl	isobutyl	methoxymethyl
979		Me	F	H	o-Cl phenyl	isobutyl	methoxymethyl
980		Me	F	H	m-Br Phenyl	isobutyl	methoxymethyl
981		Me	F	H	p-Br Phenyl	isobutyl	methoxymethyl
982		Me	F	H	o-Br Phenyl	isobutyl	methoxymethyl
983		Me	F	H	CF3	isobutyl	methoxymethyl
984		Me	F	H	cyclopentyl	isobutyl	methoxymethyl
985		Me	F	H	cyclohexyl	isobutyl	methoxymethyl
986		Me	F	H	cyclobutyl	isobutyl	methoxymethyl
987		Me	F	H	cyclopropyl	isobutyl	methoxymethyl
988		Me	F	H	Phenyl	isobutyl	methoxymethyl

989		Me	F	H	cyclopentylmethyl	isobutyl	methoxymethyl
990		Me	F	H	cyclohexylmethyl	isobutyl	methoxymethyl
991		Me	F	H	cyclobutylmethyl	isobutyl	methoxymethyl
992		Me	F	H	cyclopropylmethyl	isobutyl	methoxymethyl
993		Me	F	H	Br	isobutyl	CONHCH2
994		Me	F	H	H	isobutyl	CONHCH2
995		Me	F	H	Et	isobutyl	CONHCH2
996		Me	F	H	Cl	isobutyl	CONHCH2
997		Me	F	H	Me	isobutyl	CONHCH2
998		Me	F	H	Pr	isobutyl	CONHCH2
999		Me	F	H	i-Pr	isobutyl	CONHCH2
1000		Me	F	H	Bu	isobutyl	CONHCH2
1001		Me	F	H	i-Bu	isobutyl	CONHCH2
1002		Me	F	H	OMe	isobutyl	CONHCH2
1003		Me	F	H	OEt	isobutyl	CONHCH2
1004		Me	F	H	SMe	isobutyl	CONHCH2
1005		Me	F	H	SEt	isobutyl	CONHCH2
1006		Me	F	H	NEt2	isobutyl	CONHCH2
1007		Me	F	H	NMe2	isobutyl	CONHCH2
1008		Me	F	H	I	isobutyl	CONHCH2
1009		Me	F	H	m-OMePhenyl	isobutyl	CONHCH2
1010		Me	F	H	o-OMePhenyl	isobutyl	CONHCH2
1011		Me	F	H	p-F Phenyl	isobutyl	CONHCH2
1012		Me	F	H	o-F Phenyl	isobutyl	CONHCH2
1013		Me	F	H	m-F Phenyl	isobutyl	CONHCH2
1014		Me	F	H	2-Furanyl	isobutyl	CONHCH2
1015		Me	F	H	2-thiophenyl	isobutyl	CONHCH2
1016		Me	F	H	2-Furanylmethyl	isobutyl	CONHCH2
1017		Me	F	H	2-Thiophenylmethyl	isobutyl	CONHCH2
1018		Me	F	H	CN	isobutyl	CONHCH2
1019		Me	F	H	m-Cl phenyl	isobutyl	CONHCH2
1020		Me	F	H	p-Cl phenyl	isobutyl	CONHCH2
1021		Mo	F	H	o-Cl phenyl	isobutyl	CONHCH2
1022		Me	F	H	m-Br Phenyl	isobutyl	CONHCH2

1023		Me	F	H	p-Br Phenyl	isobutyl	CONHCH2
1024		Me	F	H	o-Br Phenyl	isobutyl	CONHCH2
1025		Me	F	H	CF3	isobutyl	CONHCH2
1026		Me	F	H	cyclopentyl	isobutyl	CONHCH2
1027		Me	F	H	cyclohexyl	isobutyl	CONHCH2
1028		Me	F	H	cyclobutyl	isobutyl	CONHCH2
1029		Me	F	H	cyclopropyl	isobutyl	CONHCH2
1030		Me	F	H	Phenyl	isobutyl	CONHCH2
1031		Me	F	H	cyclopentylmethyl	isobutyl	CONHCH2
1032		Me	F	H	cyclohexylmethyl	isobutyl	CONHCH2
1033		Me	F	H	cyclobutylmethyl	isobutyl	CONHCH2
1034		Me	F	H	cyclopropylmethyl	isobutyl	CONHCH2
1035		H	F	H	Br	isobutyl	CONHCH2
1036		H	F	H	H	isobutyl	CONHCH2
1037		H	F	H	Et	isobutyl	CONHCH2
1038		H	F	H	Cl	isobutyl	CONHCH2
1039		H	F	H	Me	isobutyl	CONHCH2
1040		H	F	H	Pr	isobutyl	CONHCH2
1041		H	F	H	i-Pr	isobutyl	CONHCH2
1042		H	F	H	Bu	isobutyl	CONHCH2
1043		H	F	H	i-Bu	isobutyl	CONHCH2
1044		H	F	H	OMe	isobutyl	CONHCH2
1045		H	F	H	OEt	isobutyl	CONHCH2
1046		H	F	H	SMe	isobutyl	CONHCH2
1047		H	F	H	SEt	isobutyl	CONHCH2
1048		H	F	H	NEt2	isobutyl	CONHCH2
1049		H	F	H	NMe2	isobutyl	CONHCH2
1050		H	F	H	I	isobutyl	CONHCH2
1051		H	F	H	m-OMePhenyl	isobutyl	CONHCH2
1052		H	F	H	o-OMePhenyl	isobutyl	CONHCH2
1053		H	F	H	p-F Phenyl	isobutyl	CONHCH2
1054		H	F	H	o-F Phenyl	isobutyl	CONHCH2
1055		H	F	H	m-F Phenyl	isobutyl	CONHCH2
1056		H	F	H	2-Furanyl	isobutyl	CONHCH2

1057		H	F	H	2-thiophenyl	isobutyl	CONHCH2
1058		H	F	H	2-Furanylmethyl	isobutyl	CONHCH2
1059		H	F	H	2-Thiophenylmethyl	isobutyl	CONHCH2
1060		H	F	H	CN	isobutyl	CONHCH2
1061		H	F	H	m-Cl phenyl	isobutyl	CONHCH2
1062		H	F	H	p-Cl phenyl	isobutyl	CONHCH2
1063		H	F	H	o-Cl phenyl	isobutyl	CONHCH2
1064		H	F	H	m-Br Phenyl	isobutyl	CONHCH2
1065		H	F	H	p-Br Phenyl	isobutyl	CONHCH2
1066		H	F	H	o-Br Phenyl	isobutyl	CONHCH2
1067		H	F	H	CF3	isobutyl	CONHCH2
1068		H	F	H	cyclopentyl	isobutyl	CONHCH2
1069		H	F	H	cyclohexyl	isobutyl	CONHCH2
1070		H	F	H	cyclobutyl	isobutyl	CONHCH2
1071		H	F	H	cyclopropyl	isobutyl	CONHCH2
1072		H	F	H	Phenyl	isobutyl	CONHCH2
1073		H	F	H	cyclopentylmethyl	isobutyl	CONHCH2
1074		H	F	H	cyclohexylmethyl	isobutyl	CONHCH2
1075		H	F	H	cyclobutylmethyl	isobutyl	CONHCH2
1076		H	F	H	cyclopropylmethyl	isobutyl	CONHCH2
1077		Cl	F	H	Br	isobutyl	CONHCH2
1078		Cl	F	H	H	isobutyl	CONHCH2
1079		Cl	F	H	Et	isobutyl	CONHCH2
1080		Cl	F	H	Cl	isobutyl	CONHCH2
1081		Cl	F	H	Me	isobutyl	CONHCH2
1082		Cl	F	H	Pr	isobutyl	CONHCH2
1083		Cl	F	H	i-Pr	isobutyl	CONHCH2
1084		Cl	F	H	Bu	isobutyl	CONHCH2
1085		Cl	F	H	I-Bu	isobutyl	CONHCH2
1086		Cl	F	H	OMe	isobutyl	CONHCH2
1087		Cl	F	H	OEt	isobutyl	CONHCH2
1088		Cl	F	H	SMe	isobutyl	CONHCH2
1089		Cl	F	H	SEt	isobutyl	CONHCH2
1090		Cl	F	H	NEt2	isobutyl	CONHCH2

1091		Cl	F	H	NMe2	isobutyl	CONHCH2
1092		Cl	F	H	I	isobutyl	CONHCH2
1093		Cl	F	H	m-OMePhenyl	isobutyl	CONHCH2
1094		Cl	F	H	o-OMePhenyl	isobutyl	CONHCH2
1095		Cl	F	H	p-F Phenyl	isobutyl	CONHCH2
1096		Cl	F	H	o-F Phenyl	isobutyl	CONHCH2
1097		Cl	F	H	m-F Phenyl	isobutyl	CONHCH2
1098		Cl	F	H	2-Furanyl	isobutyl	CONHCH2
1099		Cl	F	H	2-thiophenyl	isobutyl	CONHCH2
1100		Cl	F	H	2-Furanylmethyl	isobutyl	CONHCH2
1101		Cl	F	H	2-Thiophenylmethyl	isobutyl	CONHCH2
1102		Cl	F	H	CN	isobutyl	CONHCH2
1103		Cl	F	H	m-Cl phenyl	isobutyl	CONHCH2
1104		Cl	F	H	p-Cl phenyl	isobutyl	CONHCH2
1105		Cl	F	H	o-Cl phenyl	isobutyl	CONHCH2
1106		Cl	F	H	m-Br Phenyl	isobutyl	CONHCH2
1107		Cl	F	H	p-Br Phenyl	isobutyl	CONHCH2
1108		Cl	F	H	o-Br Phenyl	isobutyl	CONHCH2
1109		Cl	F	H	CF3	isobutyl	CONHCH2
1110		Cl	F	H	cyclopentyl	isobutyl	CONHCH2
1111		Cl	F	H	cyclohexyl	isobutyl	CONHCH2
1112		Cl	F	H	cyclobutyl	isobutyl	CONHCH2
1113		Cl	F	H	cyclopropyl	isobutyl	CONHCH2
1114		Cl	F	H	Phenyl	isobutyl	CONHCH2
1115		Cl	F	H	cyclopentylmethyl	isobutyl	CONHCH2
1116		Cl	F	H	cyclohexylmethyl	isobutyl	CONHCH2
1117		Cl	F	H	cyclobutylmethyl	isobutyl	CONHCH2
1118		Cl	F	H	cyclopropylmethyl	isobutyl	CONHCH2
1119		Me	F	H	Br	isobutyl	NHCOCH2
1120		Me	F	H	H	isobutyl	NHCOCH2
1121		Me	F	H	Et	isobutyl	NHCOCH2
1122		Me	F	H	Cl	isobutyl	NHCOCH2
1123		Me	F	H	Me	isobutyl	NHCOCH2
1124		Me	F	H	Pr	isobutyl	NHCOCH2

1125		Me	F	H	i-Pr	isobutyl	NHCOCH2
1126		Me	F	H	Bu	isobutyl	NHCOCH2
1127		Me	F	H	i-Bu	isobutyl	NHCOCH2
1128		Me	F	H	OMe	isobutyl	NHCOCH2
1129		Me	F	H	OEt	isobutyl	NHCOCH2
1130		Me	F	H	SMe	isobutyl	NHCOCH2
1131		Me	F	H	SEt	isobutyl	NHCOCH2
1132		Me	F	H	NEt2	isobutyl	NHCOCH2
1133		Me	F	H	NMe2	isobutyl	NHCOCH2
1134		Me	F	H	I	isobutyl	NHCOCH2
1135		Me	F	H	m-OMePhenyl	isobutyl	NHCOCH2
1136		Me	F	H	o-OMePhenyl	isobutyl	NHCOCH2
1137		Me	F	H	p-F Phenyl	isobutyl	NHCOCH2
1138		Me	F	H	o-F Phenyl	isobutyl	NHCOCH2
1139		Me	F	H	m-F Phenyl	isobutyl	NHCOCH2
1140		Me	F	H	2-Furanyl	isobutyl	NHCOCH2
1141		Me	F	H	2-thiophenyl	isobutyl	NHCOCH2
1142		Me	F	H	2-Furanylmethyl	isobutyl	NHCOCH2
1143		Me	F	H	2-Thiophenylmethyl	isobutyl	NHCOCH2
1144		Me	F	H	CN	isobutyl	NHCOCH2
1145		Me	F	H	m-Cl phenyl	isobutyl	NHCOCH2
1146		Me	F	H	p-Cl phenyl	isobutyl	NHCOCH2
1147		Me	F	H	o-Cl phenyl	isobutyl	NHCOCH2
1148		Me	F	H	m-Br Phenyl	isobutyl	NHCOCH2
1149		Me	F	H	p-Br Phenyl	isobutyl	NHCOCH2
1150		Me	F	H	o-Br Phenyl	isobutyl	NHCOCH2
1151		Me	F	H	CF3	isobutyl	NHCOCH2
1152		Me	F	H	cyclopentyl	isobutyl	NHCOCH2
1153		Me	F	H	cyclohexyl	isobutyl	NHCOCH2
1154		Me	F	H	cyclobutyl	isobutyl	NHCOCH2
1155		Me	F	H	cyclopropyl	isobutyl	NHCOCH2
1156		Me	F	H	Phenyl	isobutyl	NHCOCH2
1157		Me	F	H	cyclopentylmethyl	isobutyl	NHCOCH2
1158		Me	F	H	cyclohexylmethyl	isobutyl	NHCOCH2

1159		Me	F	H	cyclobutylmethyl	isobutyl	NHCOCH2
1160		Me	F	H	cyclopropylmethyl	isobutyl	NHCOCH2
1161		H	F	H	Br	isobutyl	NHCOCH2
1162		H	F	H	H	isobutyl	NHCOCH2
1163		H	F	H	Et	isobutyl	NHCOCH2
1164		H	F	H	Cl	isobutyl	NHCOCH2
1165		H	F	H	Me	isobutyl	NHCOCH2
1166		H	F	H	Pr	isobutyl	NHCOCH2
1167		H	F	H	i-Pr	isobutyl	NHCOCH2
1168		H	F	H	Bu	isobutyl	NHCOCH2
1169		H	F	H	i-Bu	isobutyl	NHCOCH2
1170		H	F	H	OMe	isobutyl	NHCOCH2
1171		H	F	H	OEt	isobutyl	NHCOCH2
1172		H	F	H	SMe	isobutyl	NHCOCH2
1173		H	F	H	SEt	isobutyl	NHCOCH2
1174		H	F	H	NEt2	isobutyl	NHCOCH2
1175		H	F	H	NMe2	isobutyl	NHCOCH2
1176		H	F	H	I	isobutyl	NHCOCH2
1177		H	F	H	m-OMePhenyl	isobutyl	NHCOCH2
1178		H	F	H	o-OMePhenyl	isobutyl	NHCOCH2
1179		H	F	H	p-F Phenyl	isobutyl	NHCOCH2
1180		H	F	H	o-F Phenyl	isobutyl	NHCOCH2
1181		H	F	H	m-F Phenyl	isobutyl	NHCOCH2
1182		H	F	H	2-Furanyl	isobutyl	NHCOCH2
1183		H	F	H	2-thiophenyl	isobutyl	NHCOCH2
1184		H	F	H	2-Furanylmethyl	isobutyl	NHCOCH2
1185		H	F	H	2-Thiophenylmethyl	isobutyl	NHCOCH2
1186		H	F	H	CN	isobutyl	NHCOCH2
1187		H	F	H	m-Cl phenyl	isobutyl	NHCOCH2
1188		H	F	H	p-Cl phenyl	isobutyl	NHCOCH2
1189		H	F	H	o-Cl phenyl	isobutyl	NHCOCH2
1190		H	F	H	m-Br Phenyl	isobutyl	NHCOCH2
1191		H	F	H	p-Br Phenyl	isobutyl	NHCOCH2
1192		H	F	H	o-Br Phenyl	isobutyl	NHCOCH2

1193		H	F	H	CF3	isobutyl	NHCOCH2
1194		H	F	H	cyclopentyl	isobutyl	NHCOCH2
1195		H	F	H	cyclohexyl	isobutyl	NHCOCH2
1196		H	F	H	cyclobutyl	isobutyl	NHCOCH2
1197		H	F	H	cyclopropyl	isobutyl	NHCOCH2
1198		H	F	H	Phenyl	isobutyl	NHCOCH2
1199		H	F	H	cyclopentylmethyl	isobutyl	NHCOCH2
1200		H	F	H	cyclohexylmethyl	isobutyl	NHCOCH2
1201		H	F	H	cyclobutylmethyl	isobutyl	NHCOCH2
1202		H	F	H	cyclopropylmethyl	isobutyl	NHCOCH2
1203		Cl	F	H	Br	isobutyl	NHCOCH2
1204		Cl	F	H	H	isobutyl	NHCOCH2
1205		Cl	F	H	Et	isobutyl	NHCOCH2
1206		Cl	F	H	Cl	isobutyl	NHCOCH2
1207		Cl	F	H	Me	isobutyl	NHCOCH2
1208		Cl	F	H	Pr	isobutyl	NHCOCH2
1209		Cl	F	H	i-Pr	isobutyl	NHCOCH2
1210		Cl	F	H	Bu	isobutyl	NHCOCH2
1211		Cl	F	H	i-Bu	isobutyl	NHCOCH2
1212		Cl	F	H	OMe	isobutyl	NHCOCH2
1213		Cl	F	H	OEt	isobutyl	NHCOCH2
1214		Cl	F	H	SMe	isobutyl	NHCOCH2
1215		Cl	F	H	SEt	isobutyl	NHCOCH2
1216		Cl	F	H	NEt2	isobutyl	NHCOCH2
1217		Cl	F	H	NMe2	isobutyl	NHCOCH2
1218		Cl	F	H	I	isobutyl	NHCOCH2
1219		Cl	F	H	m-OMePhenyl	isobutyl	NHCOCH2
1220		Cl	F	H	o-OMePhenyl	isobutyl	NHCOCH2
1221		Cl	F	H	p-F Phenyl	isobutyl	NHCOCH2
1222		Cl	F	H	o-F Phenyl	isobutyl	NHCOCH2
1223		Cl	F	H	m-F Phenyl	isobutyl	NHCOCH2
1224		Cl	F	H	2-Furanyl	isobutyl	NHCOCH2
1225		Cl	F	H	2-thiophenyl	isobutyl	NHCOCH2
1226		Cl	F	H	2-Furanylmethyl	isobutyl	NHCOCH2

1227		Cl	F	H	2-Thiophenylmethyl	isobutyl	NHCOCH2
1228		Cl	F	H	CN	isobutyl	NHCOCH2
1229		Cl	F	H	m-Cl phenyl	isobutyl	NHCOCH2
1230		Cl	F	H	p-Cl phenyl	isobutyl	NHCOCH2
1231		Cl	F	H	o-Cl phenyl	isobutyl	NHCOCH2
1232		Cl	F	H	m-Br Phenyl	isobutyl	NHCOCH2
1233		Cl	F	H	p-Br Phenyl	isobutyl	NHCOCH2
1234		Cl	F	H	o-Br Phenyl	isobutyl	NHCOCH2
1235		Cl	F	H	CF3	isobutyl	NHCOCH2
1236		Cl	F	H	cyclopentyl	isobutyl	NHCOCH2
1237		Cl	F	H	cyclohexyl	isobutyl	NHCOCH2
1238		Cl	F	H	cyclobutyl	isobutyl	NHCOCH2
1239		Cl	F	H	cyclopropyl	isobutyl	NHCOCH2
1240		Cl	F	H	Phenyl	isobutyl	NHCOCH2
1241		Cl	F	H	cyclopentylmethyl	isobutyl	NHCOCH2
1242		Cl	F	H	cyclohexylmethyl	isobutyl	NHCOCH2
1243		Cl	F	H	cyclobutylmethyl	isobutyl	NHCOCH2
1244		Cl	F	H	cyclopropylmethyl	isobutyl	NHCOCH2
1245		Me	Me	Cl	H	isobutyl	2,5-furanyl
1246	13.62	H	H	Me	Me	isobutyl	2,5-furanyl
1247	13.63	H	Cl	Me	Me	isobutyl	2,5-furanyl
1248	13.67	H	F	H	Br	isobutyl	2,5-furanyl
1249	13.68	H	F	NO_2	Br	isobutyl	2,5-furanyl
1250	13.69	H	F	NH_2	Br	isobutyl	2,5-furanyl
1251	13.70	NH_2	Cl	Me	Me	isobutyl	2,5-furanyl
1252	12.66	NH_2	F	H	cyclopropyl	isobutyl	2,5-furanyl
1253	12.67	NH_2	F	H	phenyl	isobutyl	2,5-furanyl
1254	12.68	NH_2	F	H	*p*-F-phenyl	isobutyl	2,5-furanyl
1255	12.69	NH_2	F	H	*p*-Cl-Phenyl	isobutyl	2,5-furanyl
1256	12.70	NH_2	F	H	vinyl	isobutyl	2,5-furanyl
1257	13.71	H	F	NMe_2	F	isobutyl	2,5-furanyl
1258	13.72	H	H	H	CH_2OH	isobutyl	2,5-furanyl
1259	12.71	NH_2	F	H	4-Me-pentyl	isobutyl	2,5-furanyl
1260	13.73	H	F	H	Br	H	2,5-furanyl

1261	13.74	NO_2	F	H	Br	H	2,5-furanyl
1262	13.75	H	F	NO_2	Br	H	2,5-furanyl
1263	12.73	NH_2	F	H	H	2-Et-butyl	2,5-furanyl
1264	12.72	NH_2	F	H	3,3-diMe-butyl	isobutyl	2,5-furanyl
1265	12.74	NH_2	F	H	*m*-OMe-phenyl	isobutyl	2,5-furanyl
1266	13.77	NHCO Me	F	H	Et	isobutyl	2,5-furanyl
1267	13.76	H	F	NHCO Me	Br	isobutyl	2,5-furanyl
1268	12.75	NH_2	F	H	Et	cyclopropylmethyl	2,5-furanyl
1269	12.76	NH_2	F	H	H	3-pentyl	2,5-furanyl
1270	13.79	H	F	NMe_2	Br	isobutyl	2,5-furanyl
1271	13.78	NMe_2	F	H	Et	isobutyl	2,5-furanyl
1272	12.77	H	F	F	F	isobutyl	2,5-furanyl
1273	12.78	F	F	F	H	isobutyl	2,5-furanyl
1274	13.80	H	F	Cl	Et	H	2,5-furanyl
1275	13.81	Et	Cl	F	H	isobutyl	2,5-furanyl
1276	13.83	Me	Me	Me	Me	isobutyl	2,5-furanyl
1277	13.82	Me	Me	Me	Me	H	2,5-furanyl
1278	12.79	NH_2	F	H	3-OH-propyl	isobutyl	2,5-furanyl
1279	13.86	H	H	H	H	H	$CONHCHCO_2$ Me
1280	13.84	Me	H	Me	H	H	2,5-furanyl
1281	13.85	Me	H	Me	H	isobutyl	2,5-furanyl
1282	13.87	H	Me	H	Me	isobutyl	2,5-furanyl
1283	12.80	NH_2	F	H	3-Br-propyl	isobutyl	2,5-furanyl
1284	12.81	NH_2	F	H	propyl	isobutyl	2,5-furanyl
1285	12.82	NH_2	F	H	4-Br-butyl	isobutyl	2,5-furanyl
1286	12.83	NH_2	F	H	4-Cl-butyl	isobutyl	2,5-furanyl
1287	13.88	Me	Me	Me	Me	cyclopropylmethyl	2,5-furanyl
1288	13.89	Me	Me	Cl	H	ethyl	2,5-furanyl
1289	13.90	Me	Me	Cl	H	4-Br-butyl	2,5-furanyl
1290	12.85	Me	Me	Cl	H	cyclopropylmethyl	2,5-thionyl
1291	13.91	Me	Me	Cl	Br	H	2,5-furanyl

1292	13.92	Me	Me	Cl	Br	isobutyl	2,5-furanyl
1293	15.1	NH_2	F	H	Br	isobutyl	methoxymethyl
1294	12.84	NH_2	F	H	3-(*N,N*-dimethyl)propylamine	isobutyl	2,5-furanyl
1295	13.96	Br	Cl	Me	Me	isobutyl	2,5-furanyl
1296	13.94	H	Cl	H	H	*n*-butylamine	2,5-furanyl
1297	13.95	H	H	Cl	H	*n*-butylamine	2,5-furanyl
1298	13.96	Me	Cl	H	H	isobutyl	2,5-furanyl
1299		H	Me	Cl	H	isobutyl	2,5-furanyl
1300		Cl	Me	Cl	H	isobutyl	2,5-furanyl
1301		NH_2	F	H	Et	isobutyl	methoxymethyl
1302		NH_2	F	H	4-bromobutyl	isobutyl	methoxymethyl
1303		NH_2	F	H	3-bromopropyl	isobutyl	methoxymethyl
1304		NH_2	F	H	4-chlorobutyl	isobutyl	methoxymethyl
1305		NH_2	F	H	3-chloropropyl	isobutyl	methoxymethyl
1306		NH_2	F	H	3-hydroxypropyl	isobutyl	methoxymethyl
1307		NH_2	F	H	4-hydroxybutyl	isobutyl	methoxymethyl
1308		NH_2	F	H	3-(*N,N*-dimethyl)propylamine	isobutyl	methoxymethyl
1309	17.1	H	H	H	H	H	$-CONHCH_2-$
1310		NH_2	F	H	H	isobutyl	methoxymetthyl
1311	12.86	NH_2	F	H	Et	H	2,5-furanyl

More preferred are the following compounds from Table 1 and salts and prodrugs thereof:

41, 42, 43, 53, 55, 56, 57, 58, 59, 60, 62, 63, 87, 88, 128, 281, 282, 322, 354, 484, 485, 490, 491, 494, 504, 506, 568, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 654, 696, 697, 698, 699, 700, 701, 705, 706, 707, 708, 709, 710, 1248, 1249, 1251, 1252, 1253, 1254, 1255, 1256, 1259, 1263, 1264, 1265, 1268, 1269, 1273, 1276, 1277, 1278, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1293, 1294, 1295, 1298.

Most preferred are the following compounds from Table 1 and salts and prodrugs thereof:

5-Fluoro-7-bromo-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4,5-Dimethyl-6-chloro-1-isopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole;
6-Chloro-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole;
5,6-Difluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4-Amino-5,7-dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4-Amino-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole;
4-Amino-5-fluoro-7-chloro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-6-chloro-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-6-methylthio-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-6-chloro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
1-isobutyl-4-methyl-5-chloro-2(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-isobutylbenzimidazol-2-ylmethyleneoxymethylphosphonic acid;
4-Amino-5,6-difluoro-7-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-neopentyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-cyclobutylmethyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole;
4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(1-hydroxy-1-phosphonopropyl)benzimidazole; and
4-Amino-5-fluoro-7-isopropyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-cyclopropyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-phenyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-(4-methylpentyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-(3-hydroxypropyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-(3-bromopropyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-(4-bromobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-(4-chlorobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

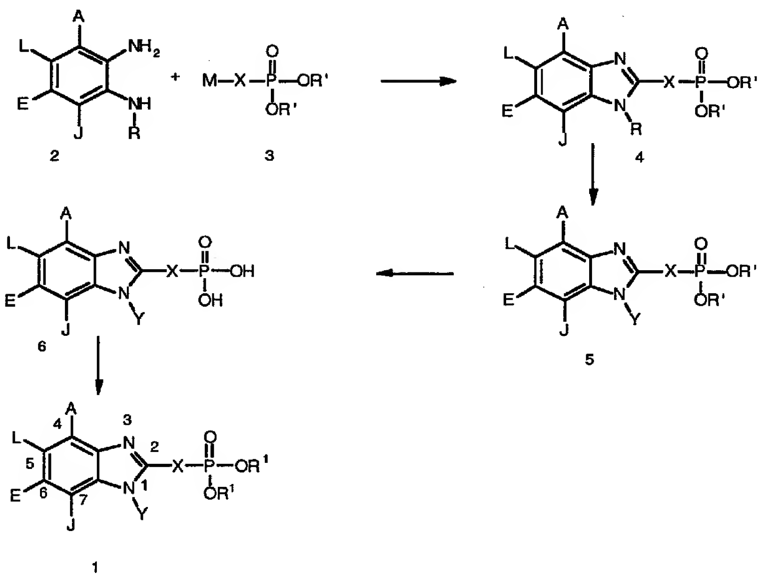
4-Amino-5-fluoro-7-(3-N,N-dimethylpropylamine)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole.

4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(1-methoxymethyl-3-phosphono)benzimidazole.

4-Amino-5-fluoro-1-isobutyl-2-(1-methoxymethyl-3-phosphono)benzimidazole.

Synthesis of Compounds of Formula 1

Synthesis of the compounds encompassed by the present invention typically includes some or all of the following general steps: (1) synthesis of the prodrug ; (2) phosphonate deprotection; (3) substitution of the heterocycle; (4) substitution or modification of 2-substituent; (5) cyclization to generate benzimidazole ring system; (6) synthesis of the linker-PO_3R_2; and (7) synthesis of the substituted 1,2-phenylenediamine. A detailed discussion of each step is given below.



1) Preparation of Phosphonate Prodrugs

Prodrug esters can be introduced at different stages of the synthesis. Most often, these prodrugs are made from the phosphonic acids of formula 6 because of their lability. Advantageously, these prodrug esters can be introduced at an earlier stage, provided they can withstand the reaction conditions of the subsequent steps.

Compounds of formula 6, can be alkylated with electrophiles (such as alkyl halides, alkyl sulfonates, etc) under nucleophilic substitution reaction conditions to give phosphonate esters. For example, prodrugs of formula 1, where R^1 is acyloxymethyl group can be synthesized through direct alkylation of the free phosphonic acid of formula 6 with the desired acyloxymethyl halide (e.g. $Me_3CC(O)OCH_2I$; Elhaddadi, et al *Phosphorus Sulfur*, **1990**, *54(1-4)*: 143; Hoffmann, *Synthesis*, **1988**, 62) in presence of base e.g. *N, N'*-dicyclohexyl-4-morpholinecarboxamidine, Hunigs base, etc. in polar aprotic solvents such as DMF (Starrett, et al, *J. Med. Chem.*, **1994**, 1857). These carboxylates include but are not limited to acetate, propionate, isobutyrate, pivalate, benzoate, and

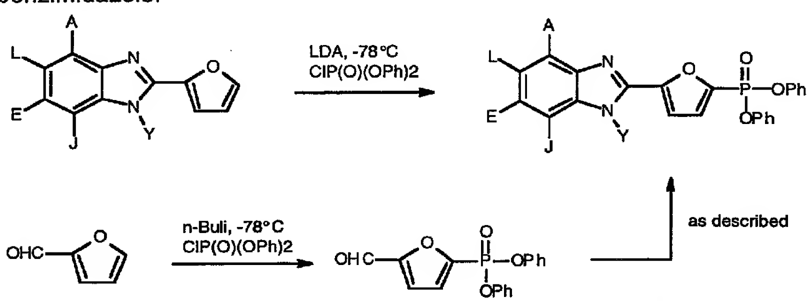
other carboxylates. Alternately, these acyloxymethylphosphonate esters can also be synthesized by treatment of the nitrophosphonic acid (A is NO_2 in formula 6; Dickson, et al, *J. Med. Chem.*, **1996**, *39*: 661; Iyer, et al, *Tetrahedron Lett.*, **1989**, *30*: 7141; Srivastva, et al, *Bioorg. Chem.*, **1984**, *12*: 118). This methodology can be extended to many other types of prodrugs, such as compounds of formula 1 where R1 is 3-phthalidyl, 2-oxo-4,5-didehydro-1,3-dioxolanemethyl, and 2-oxotetrahydrofuran-5-yl groups, etc. (Biller and Magnin (US 5,157,027); Serafinowska et al. (J. Med. Chem. *38*: 1372 (1995)); Starrett et al. (J. Med. Chem. *37*: 1857 (1994)); Martin et al. J. Pharm. Sci. *76*: 180 (1987); Alexander et al., Collect. Czech. Chem. Commun, *59*: 1853 (1994)); and EPO 0632048A1). *N,N*-Dimethylformamide dialkyl acetals can also be used to alkylate phosphonic acids (Alexander, P., et al *Collect. Czech. Chem. Commun.*, **1994**, *59*, 1853).

Alternatively, these phosphonate prodrugs or phosphoramidates can also be synthesized, by reaction of the corresponding dichlorophosphonate and an alcohol or an amine (Alexander, et al, *Collect. Czech. Chem. Commun.*, **1994**, *59*: 1853). For example, the reaction of dichlorophosphonate with phenols and benzyl alcohols in the presence of base (such as pyridine, triethylamine, etc) yields compounds of formula **1** where R^1 is aryl (Khamnei, S., et al *J. Med. Chem.*, **1996**, *39*: 4109; Serafinowska, H.T., et al *J. Med. Chem.*, **1995**, *38*: 1372; De Lombaert, S., et al *J. Med. Chem.*, **1994**, *37*: 498) or benzyl (Mitchell, A.G., et al *J. Chem. Soc. Perkin Trans. 1*, **1992**, *38*: 2345). The disulfide-containing prodrugs, reported by Puech et al., *Antiviral Res.*, **1993**, *22*: 155, can also be prepared from dichlorophosphonate and 2-hydroxyethyl disulfide under standard conditions.

Such reactive dichlorophosphonate intermediates, can be prepared from the corresponding phosphonic acids and chlorinating agents e.g. thionyl chloride (Starrett, et al, *J. Med. Chem.*, **1994**, 1857), oxalyl chloride (Stowell, et al, *Tetrahedron Lett.*, **1990**, *31*: 3261), and phosphorus pentachloride (Quast, et al, *Synthesis*, **1974**, 490). Alternatively, these dichlorophosphonates can also be generated from disilylphosphonate esters (Bhongle, et al, *Synth. Commun.*, **1987**, *17*: 1071) and dialkylphosphonate esters (Still, et al, *Tetrahedron Lett.*, **1983**, *24*: 4405; Patois, et al, *Bull. Soc. Chim. Fr.*, **1993**, *130*: 485).

Furthermore, these prodrugs can be prepared from Mitsunobu reactions (Mitsunobu, *Synthesis*, **1981**, 1; Campbell, *J.Org. Chem.*, **1992**, *52*: 6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, *Collect. Czech. Chem. Commun.*, **1994**, *59*: 1853; Casara, et al, *Bioorg. Med. Chem. Lett.*, **1992**, *2*: 145; Ohashi, et al, *Tetrahedron Lett.*, **1988**, *29*: 1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, et al, *Tetrahedron Lett.*, **1993**, *34*: 6743). The prodrugs of formula 1 where R^1 is the cyclic carbonate or lactone or phthalidyl can also be synthesized by direct alkylation of free phosphonic acid with the desired halides in the presence of base such as NaH or diisopropylethylamine (Biller and Magnin US 5,157,027; Serafinowska et al. J. Med. Chem. *38*: 1372 (1995); Starrett et al. J. Med. Chem. *37*: 1857 (1994); Martin et al. *J. Pharm. Sci. 76*: 180 (1987); Alexander et al., Collect. Czech. Chem. Commun, *59*: 1853 (1994); and EPO 0632048A1).

R^1 can also be introduced at an early stage of the synthesis. For example, compounds of formula 1 where R^1 is phenyl can be prepared by phosphorylation of 2-furanyl benzimidazole subjected to a strong base (e.g. LDA) and chlorodiphenyl phosphonate. Alternatively, such compounds can be prepared by alkylation of lithiated furfuraldehyde followed by ring closure to the benzimidazole.



It is envisioned that compounds of formula 1 can be mixed phosphonate esters (e.g. phenyl benzyl phosphonate esters, phenyl acyloxyalkyl phosphonate esters, etc). For example, the chemically combined phenyl-benzyl prodrugs are reported by Meier, et al. *Bioorg. Med. Chem. Lett.*, **1997**, *7*: 99.

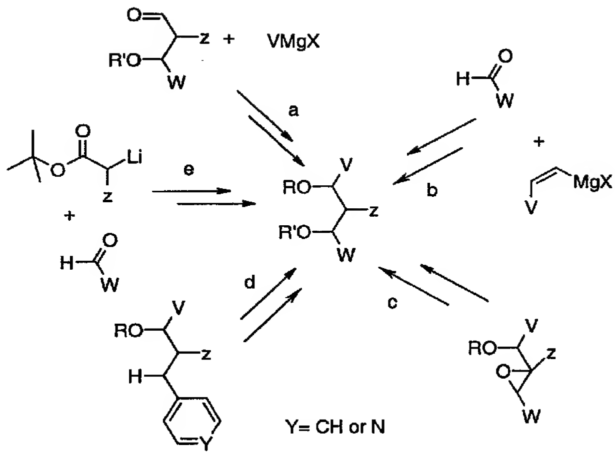
The substituted cyclic propyl phosphonate esters of formula 1, can be synthesized by reaction of the corresponding dichlorophosphonate and the substituted 1,3-propane diol. The following are some methods to prepare the substituted 1,3-propane diols.

Synthesis of the 1,3-Propane Diols Used in the Preparation of Certain Prodrugs

The discussion of this step includes various synthetic methods for the preparation of the following types of propane-1,3-diols: i) 1-substituted; ii) 2-substituted; and iii) 1,2- or 1,3-annulated. Different groups on the prodrug part of the molecule *i.e.*, on the propane diol moiety can be introduced or modified either during the synthesis of the diols or after the synthesis of the prodrugs.

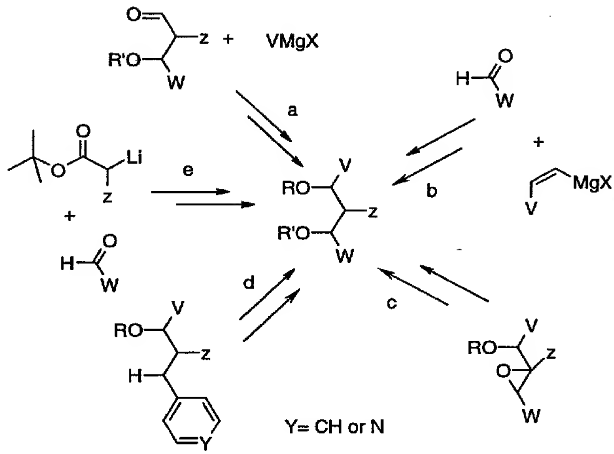
i) 1-Substituted 1,3-Propane Diols

Propane-1,3-diols can be synthesized by several well known methods in the literature. Aryl Grignard additions to 1-hydroxypropan-3-al gives 1-aryl-substituted propane-1,3-diols (path a). This method will enable conversion of various substituted aryl halides to 1-arylsubstituted-1,3-propane diols (Coppi, et. al., *J. Org. Chem.*, **1988**, *53*, 911). Aryl halides can also be used to synthesize 1-substituted propanediols by Heck coupling of 1,3-diox-4-ene followed by reduction and hydrolysis (Sakamoto, et. al., *Tetrahedron Lett.*, **1992**, *33*, 6845). A variety of aromatic aldehydes can be converted to 1-substituted-1,3-propane diols by vinyl Grignard addition followed by hydroboration (path b). Substituted aromatic aldehydes are also useful for lithium-t-butylacetate addition followed by ester reduction (path e) (Turner., *J. Org. Chem.*, **1990**, *55* 4744). In another method, commercially available cinnamyl alcohols can be converted to epoxy alcohols under catalytic asymmetric epoxidation conditions. These epoxy alcohols are reduced by Red-Al to result in enantiomerically pure propane-1,3-diols (path c). Alternatively, enantiomerically pure 1,3-diols can be obtained by chiral borane reduction of hydroxyethyl aryl ketone derivatives (Ramachandran, et. al., *Tetrahedron Lett.*, **1997**, *38* 761). Pyridyl, quinoline, and isoquinoline propan-3-ol derivatives can be oxygenated to 1-substituted propan-1,3-diols by N-oxide formation followed by rearrangement under acetic anhydride conditions (path d) (Yamamoto, et. al., *Tetrahedron* , **1981**, *37*, 1871).



ii) 2-Substituted 1,3-Propane Diols:

Various 2-substituted propane-1,3-diols can be made from commercially available 2-(hydroxymethyl)-1,3-propane diol. Triethyl methanetricarboxylate can be converted to the triol by complete reduction (path a) or diol-monocarboxylic acid derivatives can be obtained by partial hydrolysis and diester reduction (Larock, *Comprehensive Organic Transformations*, VCH, New York, **1989**). Nitrotriol is also known to give the triol by reductive elimination (path b) (Latour, et. al., *Synthesis*, **1987**, *8*, 742). The triol can be derivatized as a mono acetate or carbonate by treatment with alkanoyl chloride, or alkylchloroformate, respectively (path d) (Greene and Wuts, *Protective Groups in Organic Synthesis*, John Wiley, New York, **1990**). Aryl substitution effected by oxidation to the aldehyde followed by aryl Grignard additions (path c) and the aldehyde can also be converted to substituted amines by reductive amination reactions (path e).



iii) Annulated 1,3-Propane Diols:

Prodrugs of formula 1 where V - Z or V - W are fused by three carbons are made from cyclohexane diol derivatives. Commercially available *cis, cis*-1,3,5-cyclohexane triol can be used for prodrug formation. This cyclohexanetriol can also be modified as described in the case of 2-substituted propan-1,3-diols to give various analogues. These modifications can either be made before or after formation of prodrugs. Various 1,3-cyclohexane diols can be made by Diels-Alder methodology using pyrone as the diene (Posner, et. al., *Tetrahedron Lett.*, **1991**, *32,* 5295). Cyclohexyl diol derivatives are also made by nitrile oxide olefin-additions (Curran, et. al., *J. Am. Chem. Soc.*, **1985**, *107*, 6023). Alternatively, cyclohexyl precursors can be made from quinic acid (Rao, et. al., *Tetrahedron Lett.*, **1991**, *32,* 547.)

2) Phosphonate Deprotection

Compounds of formula 6, may be prepared from phosphonate esters of formula 5, using known phosphate and phosphonate ester cleavage conditions. In general, silyl halides have been used to cleave the various phosphonate esters, followed by mild hydrolysis of the resulting silyl phosphonate esters to give the desired phosphonic acids. Depending on the stability of the products,

these reactions are usually accomplished in the presence of acid scavengers such as 1,1,1,3,3,3-hexamethyldisilazane, 2,6-lutidine, etc. Such silyl halides include, chlorotrimethylsilane (Rabinowitz, *J. Org. Chem.*, **1963**, *28*: 2975), bromotrimethylsilane (McKenna, et al, *Tetrahedron Lett.*, **1977**, 155), iodotrimethylsilane (Blackburn, et al, *J. Chem. Soc., Chem. Commun.*, **1978**, 870). Alternately, phosphonate esters can be cleaved under strong acid conditions, (e.g HBr, HCl, etc.) in polar solvents, preferably acetic acid (Moffatt, et al, *U.S. Patent 3,524,846*, **1970**) or water. These esters can also be cleaved via dichlorophosphonates, prepared by treating the esters with with halogenating agents e.g. phosphorus pentachloride, thionyl chloride, BBr_3, etc.(Pelchowicz, et al, *J. Chem. Soc.*, **1961**, 238) followed by aqueous hydrolysis to give phosphonic acids. Aryl and benzyl phosphonate esters can be cleaved under hydrogenolysis conditions (Lejczak, et al, *Synthesis*, **1982**, 412; Elliott, et al, *J. Med. Chem.*, **1985**, *28*: 1208; Baddiley, et al, *Nature*, **1953**, *171*: 76) or dissolving metal reduction conditions(Shafer, et al, *J. Am. Chem. Soc.*, **1977**, *99*: 5118). Electrochemical (Shono, et al, *J. Org. Chem.*, **1979**, *44*: 4508) and pyrolysis (Gupta, et al, *Synth. Commun.*, **1980**, *10*: 299) conditions have also been used to cleave various phosphonate esters.

3) Substitution of the Heterocycle

The benzimidazole ring system of formula 4, may require further elaboration to provide desired compounds of formula 5.

i) Substitution of the Phenyl Ring

Electrophilic and nucleophilic substitution reactions enable incorporation of the desired substitutions encompassed by the formula 5. (March, *Advanced Organic Chemistry* by, Wiley-Interscience, **1992**, 501-521; 641-654). For example, treatment of the compounds of formula 4 , where A is NH_2, L and J are hydrogens with NBS, NCS or NIS in halogenated solvents such as carbon tetrachloride or chloroform gives halo-substituted compounds of formula 5 (L and/or J are halogens). Compounds of formula 5, where A is NO_2, L and/or J are alkenyl, alkynyl, alkyl, or aryl groups, and Y is H or alkyl, may be prepared from compounds of formula 4, where A is NO_2, R is H or alkyl, and L and/or J are halogens, preferably bromide or iodide, through Stille coupling (Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*: 508-524). Treatment of the compounds of formula 4, where A is NO_2, and L and/or J are bromides, with a coupling reagent (e.g. tributyl(vinyl)tin, phenylboronic acid, propargyl alcohol, *N,N*-propargyl

amine etc.) in presence of palladium catalyst [e.g. bis(triphenylphosphine)palladium (II)chloride, tetrakis(triphenylphosphine) palladium(0), etc.] in solvent, such as DMF, toluene, etc. provides the coupling products. The compounds thus obtained can be modified as needed. For example vinyl or propargyl alcohol derivatives can be hydrogenated to give the ethyl or propyl alcohol derivatives respectively. These alcohols can be further modified as required *via* alkyl halides (ref. Wagner et al. *Tetrahedron Lett.* **1989**, *30,* 557.) or alkyl sulfonates etc. to a number of substituted alkyls such as amino alkyl compounds by subjecting them to nucleophilic substitution reactions (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 293-500). Alternatively, these substitutions can also be done by metal exchange followed by quenching with an appropriate nucleophile (Jerry March, *Advanced Organic Chemistry* , Wiley-Interscience, **1992**, 606-609). Nucleophilic addition reactions can also be useful in preparing compounds of formula 5. For example, when A is NO_2, L and/or J are halogens, nucleophiles such as alkoxides, thiols, amines, etc. provide the halogen displacement products. (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 649-676). Another example is addition reactions, for example cyclopropanation (Vorbruggen et al,*Tetrahedron Lett.* **1975**, 629), on the olefins(e.g. styryl type) synthesized through Stille coupling.

If required, these substituted compounds can be further modified to the desired products. For example, reduction of the NO_2 to NH_2 may be done in many different ways, e.g. Pd/C, H_2, aq. $Na_2S_2O_4$, etc. (Larock, *Comprehensive Organic Transformations* , VCH, 412-415). These primary aromatic amines can also be modified as needed. For example, N-acetyl derivatives can be prepared by treatment with acetyl chloride or acetic anhydride in the presence of a base such as pyridine. The mono- or di-alkylamines can be synthesized by direct alkylation, using a base such as NaH in polar solvents such as DMF or by reductive alkylation methods (ref. Abdel-Magid et al. *Tetrahedron Lett.* **1990**, *31*, 5595; also see ref. March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 898-900 for more methods).

ii) Alkylation of the Imidazole Ring

Alkylation of the heterocycle of formula 4, (where R and J are both H) is obtained through two distinct methods that are amenable to a large number of electrophiles: a) Mitsunobu alkylation, and b) base alkylation.

a) Mitsunobu Alkylation

Alkylation of the benzimidazole ring system of formula 4, is achieved by treatment of an alcohol, triphenylphosphine and dialkylazodicarboxylate with heterocycle and a non-nucleophilic base such as Hunigs base in polar solvents such as CH_3CN (Zwierzak et al, *Liebigs Ann. Chem.* **1986**, 402).

b) Base Alkylation

Alternately, the benzimidazole ring system of formula 4 can be deprotonated with a suitable base, preferably cesium carbonate in a polar aprotic solvent such as DMF, and the resulting anion is alkylated with an appropriate electrophilic component Y-L', where L' is a leaving group preferably bromide or iodide.

4) Substitution or Modification of a 2-substituent

Another key intermediate envisioned in the synthesis of compounds of formula 4 are substituted 2-methylbenzimidazoles. These compounds are readily prepared by condensing Ac_2O with the appropriate 1,2-phenylenediamine (Phillips, *J. Chem. Soc.,* **1928**, *29*: 1305). These compounds are useful in the synthesis of formula 1, wherein X is CH_2ZCH_2(Z=O,S,NH). For example, compounds where Z=O are readily prepared by treatment of the 2-methylbenzimidazole with a halogenating agent such as NBS followed by reaction with the α-hydroxy phosphonate ester (also see section 6, Synthesis of the Linker-PO_3R_2). Alternately, a heterosubstituted methyl phosphonates can also be prepared by displacement reactions on phosphonomethyl halides or sulfonates (Phillion et al, *Tetrahedron Lett.*, **1986**, *27*: 1477.) with an appropriate nucleophile e.g. 2-hydroxylmethylbenzimidazole compound which can be prepared using a variety of methods, including oxidation of the substituted 2-methylbenzimidazoles.

Similarly, compounds of formula 1, where X is carboxypropyl or sulfonopropyl can be prepared from the reaction of 2-(2-iodoethyl) benzimidazole and corresponding phosphonomethylcarboxylate or phosphonomethylsulfonate (Carretero et al., *Tetrahedron*, **1987**, 43, 5125) in the presence of base such as NaH in polar aprotic solvents such as DMF. The

substituted 2-(2-iodoethyl) benzimidazole can be prepared from condensation of the corresponding substituted diamine and 3-halopropanaldehyde. Also see ref. Magnin, D. R. et al. *J. Med. Chem.* **1996**, 39, 657 for the preparation of α-phosphosulfonic acids.

The componds of formula 4 where X is all carbon e.g. -$(CH_2)_3$- can be prepared by Stille coupling (Stille *Angew. Chem. Int. Ed. Engl.* **1986,** *25*: 508-524) of the dialkylphosphopropenyl tributylstanne (*J. Org. Chem.* **1993**, *58*: 6531.) and appropriate 2-bromobenzimidazole (Mistry, et al, *Tetrahedron Lett.*, **1986**, *27*: 1051).

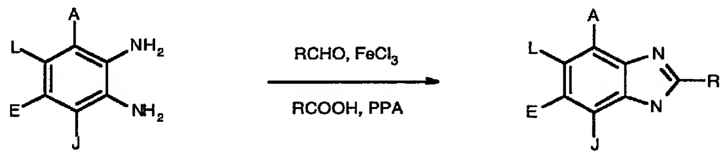
The componds of formula 4 where X is an amide linker e.g. -$CONHCH_2$- can be synthesized using the following two steps. Treatment of the appropriate 1,2-phenylenediamine with trihalomethylacetamidate preferably trichloromethylacetamidate in polar solvent such as acetic acid followed by hydrolysis of the trihalomethyl group with strong aqueous base (e.g. KOH) gives the benzimidazole-2-carboxylic acid (*Eur. J. Med. Chem.*, **1993**, *28*: 71). Condensation of the acid with an amino phosphonate e.g. diethyl(aminomethyl)phosphonate in presence of a coupling agent (e.g. pyBOP) in a polar solvent such as methylene chloride provides the amide linked phosphonate.

The componds of formula 4 where X is an amide linker e.g. -$NHCOCH_2$- can be synthesized using the following two steps. Treatment of the appropriate 1,2-phenylenediamine with cyanogenbromide (Johnson, et al, *J. Med. Chem.*, **1993**, *36*: 3361) in polar solvent such as MeOH gives the 2-amino benzimidazole. Condensation of the 2-aminobenzimidazole with a carboxylic acid e.g. diethyl(carboxymethyl)phosphonate using standard coupling conditions (Klausner, et al, *Synthesis,* **1972**, 453) provides the amide linked phosphonate. The 2-aminobenzimidazoles can also be prepared from the 2-bromobenzimidazole *via* the 2-azidobenzimidazole using known methods (*Chem. Rev.* **1988,** *88*: 297).

5) Cyclization to Generate Benzimidazole Ring System

The benzimidazole ring systems of formula 4 is preferably assembled by condensation of substituted 1,2-phenylenediamines with an aldehyde (RCHO, where R is e.g. aliphatic, heteroaliphatic, aromatic or heteroaromatic etc.) using known methods; (a) in presence of Fe^{3+} salts, preferably $FeCl_3$, in polar solvents such as DMF, EtOH etc., (b) reflux in non-polar solvents such as toluene

followed by oxidation, preferably with iodine (Bistocchi et al, *Collect. Czech. Chem. C*, **1985**, *50(9)*: 1959.)., (c) in cases of protected aldehydes, the first condensation can be achieved in the presence of a dilute inorganic acid, preferably 10 % H_2SO_4, in polar solvents such as THF, followed by oxidation with I_2. Alternatively, this coupling can be achieved with an anhydride (RCOOCOR), a carboxylic acid (RCOOH), with a nitrile (RCN) by methods reported by Hein, et al, *J. Am. Chem. Soc.* **1957**, *79,* 427.; and Applegate, et al, US 5,310,923; or imidates (R-C(=NH)-OEt) ref. Maryanoff, et al. *J. Med. Chem.* **1995**, *38*: 16.



Advantageously, these benzimidazole ring systems can be constructed using solid phase synthesis (ref: Phillips et al. *Tet. Lett.*, **1996**, *37*: 4887; Lee et al., *Tet. Lett*, **1998**: *35*: 201.

6) Synthesis of the Linker-PO_3R_2

Coupling of aromatic or aliphatic aldehydes, ketals or acetals of aldehydes, and acid derivatives with attached phophonate esters are particularly well suited for the synthesis of compounds of formula 1.

i) Preparation of Aryl and Heteroaryl Phosphonate Esters

Aryl functionalized phosphonate linkers can be prepared by lithiation of an aromatic ring using methods well described in literature (Gschwend, *Org. React.* **1979**, *26*, 1; Durst, *Comprehensive Carbanion Chemistry*, Vol. 5, Elsevier, New York, **1984**) followed by addition of phosphorylating agents (e.g. $ClPO_3R_2$). Phosphonate esters are also introduced by Arbuzov-Michaelis reaction of primary halides (Brill, T. B., *Chem Rev.*, **1984**, *84*: 577). Aryl halides undergo Ni^{2+} catalysed reaction with trialkylphosphites to give aryl phosphonate containing compounds (Balthazar, et al, *J. Org. Chem.*, **1980**, *45*: 5425). Aromatic triflates are known to result in phosphonates with $ClPO_3R_2$ in the presence of a palladium catalyst (Petrakis, et al, J. Am. Chem. Soc., **1987**, *109*:

2831; Lu, et al, *Synthesis*, **1987**, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin, *Tetrahedron Lett.*, **1981**, *22*: 3375; Casteel, et al, *Synthesis*, **1991**, 691). Using the same method described above, arylphosphate esters, where X is aryloxy, can also be made. N-Alkoxy aryl salts with alkali metal derivatives of dialkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore, *J. Org. Chem.*, **1970**, *35*: 4114).

In the linker phosphonate synthesis, aldehyde, ketone, or carboxylic acid functionalities can also be introduced after the phosphonate ester is formed. A lithiation reaction can be used to incorporate the aldehyde or ketone functionalities, although other methods known to generate aromatic aldehydes or ketones can be envisioned as well (e.g. Vilsmeier-Hack reaction, Reimar-Teimann reaction etc.; Pizey, *Synthetic reagents*, **1974**, *1*: 1; Wynberg, H., et al, *Org. React.* **1982**, *28*: 1; palladium catalyzed coupling reaction of acid halides and organotin compounds). For example, for the lithiation reaction, the lithiated aromatic ring can be treated with reagents that directly generate the aldehyde (*e.g.* DMF, HCOOR, *etc.*)(Einchorn, J., et al, *Tetrahedron Lett.*, **1986**, *27*: 1791), or the ketone (e.g. Weinreb's amide, RCOOR'). The lithiated aromatic ring can also be treated with reagents that lead to a group that is subsequently transformed into the aldehyde or ketone group using known chemistry (synthesis of aldehyde and ketone from alcohol, ester, cyano, alkene, *etc.*). It is also envisioned that the sequence of these reactions can be reversed, *i.e.* the aldehyde and ketone moieties can be incorporated first, followed by the phosphorylation reaction. The order of the reaction will depend on reaction conditions and protecting groups. Prior to the phosphorylation it is also envisioned that it may be advantageous to protect the aldehyde or ketone using well-known methods (acetal, aminal, hydrazone, ketal, etc.), and then the aldehyde or ketone is unmasked after phosphorylation. (*Protective groups in Organic Synthesis*, Greene, T. W., **1991**, Wiley, New York).

The above mentioned methods can also be extended to the heteroaryl linkers e.g. pyridine, furan, thiophene etc.

ii) Preparation of Aliphatic and Heteroaliphatic Phosphonate Esters

Compounds of formula 3, where M is CO_2R and X is alkyl can be synthesized using reactions well known in the art. Trialkyl phosphites attack lactones at the β-carbon atom, causing the alkyl-oxygen cleavage of the lactone ring, to yield alkyl(dialkylphosphono)esters. This reaction can be applied to many types of lactones such as β-lactones, γ-lactones etc. as reported by McConnell et al, *J. Am. Chem. Soc.*, **1956**, *78*, 4453. Alternatively, these type of compounds can be synthesized using the Arbuzov reaction (*Chem. Rev.* **1984**, *84*: 577). The linkers Ar(Z)alkyl phosphonates (Ar=aryl; Z=O,S etc.) can be prepared from the reaction of substituted aryls e.g. salicylaldehyde with an appropriate phosphonate electrophile [$L(CH2)_nPO_3R_2$, L is a leaving group, preferably iodine; Walsh et al, *J. Am. Chem. Soc.*, **1956**, *78*, 4455.] in the presence of a base, preferably K_2CO_3 or NaH, in a polar aprotic solvent, such as DMF or DMSO. For the preparation of α-phosphosulfonic acids see ref. Magnin, D. R. et al. *J. Med. Chem.* **1996,** *39,* 657; and ref. cited therein.

Compounds of formula 3, where M is CO_2R or CHO and X is carbonylalkyl can be synthesized from the acid chlorides (for example H(O)C-$CH_2C(O)Cl$) and $P(OEt)_3$ (*Chem. Rev.* **1984**, 84: 577). These α-ketophosphonates can be converted to the α-hydroxyphoshonates and α,α-dihalophosphonates (ref. Smyth, et al. *Tett. Lett.*, **1992**, 33, 4137). For another method of synthesizing these α,α-dihalophosphonates see the ref. Martin et al. *Tett. Lett.* **1992**, 33, 1839.

Compounds of formula 3, where X is a heteroalkyl linker e.g. -CH_2ZCH_2- where Z=O,S etc. and M is aldehyde or its protected form such as dialkyl acetal (*Protective groups in Organic Synthesis*, Greene, T. W., **1991**, Wiley, New York) can be prepared by nucleophilic substitution reactions (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 293-500) to give unsymmetrical ethers. For example linkers of formula 3, where X is alkyloxymethyl can be synthesized through direct alkylation of the hydroxymethyl phosphonate ester, with the desired alkyl halide [$L(CH_2)_nCH(OMe)_2$, L is a leaving group, preferably bromine or iodine] in the presence of a base, preferably NaH, in a polar aprotic solvent, such as DMF or DMSO. These methods can be extended to the heteroalkyl linkers e.g. -CH_2ZCH_2- where Z=S, NH etc.

7) Synthesis of the Substituted 1,2-phenylenediamine

1,2-Phenylenediamines utilized in the preparation of compounds of formula 1, can be synthesized using methods well known in the art.

(a) Compounds of formula 2, where R is H, can be synthesized from simple aromatic compounds. Most aromatic compounds may be nitrated given the wide variety of nitrating agents available(March, *Advanced Organic Chemistry*, Wiley-Interscience, **1992**, 522-525). Primary aromatic amines are often N-acetylated before nitration by treatment with acetyl chloride or acetic anhydride. Nitration of the these acetanilide derivatives using 60 % HNO_3 and H_2SO_4 (Monge et al, *J. Med. Chem.*, **1995**, *38*: 1786; Ridd *Chem. Soc. Rev.* **1991**, *20*: 149-165), followed by deprotection by strong acid (e.g. H_2SO_4, HCl, etc.), and hydrogenation (e.g. H_2, Pd/C; $Na_2S_2O_4$; etc.) of the resulting 2-nitroanilines provides the desired substituted 1,2-phenylenediamines. Similarly, substituted arylhalides (F,Cl,Br,I) can also be nitrated to provide α-halonitroaryl compounds followed by nucleophilic addition (e.g. NH_3, NH_2OH, etc) and reduction to generate the diamines.

(b) Diamines of formula 2, where A is NO_2 and R is H, can be produced using the method of Grivas et. al., *Synthesis* **1992,** 1283 and Tian et al *J. Chem. Soc. Perkin Trans* 1, **1993**, 257 and an appropriate o-nitroaniline. A variety of reactions can be used to substitute the o-nitroaniline. For example halogenation of the nitroaniline (e.g. Br_2 ,Cl_2 etc.) gives the corresponding 4,6-disubstituted or monosubstituted nitroaniline which can be further modified at a later stage. The nitro group can be reduced with number of reagents preferably sodium dithionite to provide the corresponding diamine. This diamine is then subjected to nitration conditions by first generating the 2,1,3-benzoselenadiazole with selenium dioxide followed by nitric acid. Substituted nitro-1,2-phenylenediamines are generated by treatment of the nitro-2,1,3-benzoselenadiazole with aqueous hydrogen iodide or NH_3/H_2S (Nyhammar et al, *Acta, Chem. Scand.* **1986,** *B40*: 583). Other methods to simultaneously protect the diamine are also envisioned.

(c) The componds of formula 2, where R is alkyl or aryl, can be synthesized using the method of Ohmori et al, *J. Med. Chem.* **1996,** *39*: 3971. Nucleophilic substitution of the o-halonitrobenzenes by treatment with various alkylamines followed by reduction (e.g. $Na_2S_2O_4$) of the nitro group provides the desired compounds. Alternately, the componds of formula 2, where R is H, can be

synthesized from these o-halonitrobenzenes *via* o-azidonitrobenzenes followed by reduction of the nitro group to provide the desired compound.

(d) Alternately, diamines of formula 2 where R is not H are prepared by reductive alkylation of the o-nitroanilines with various aldehydes(e.g. akyl, aryl etc.) in the presence of a reducing agent preferably $NaB(OAc)_3$ followed by reduction (e.g. $Na_2S_2O_4$; Pd/C, H_2 etc.) of the nitro group (Magid et al *Tetrahedron Lett.* **1990,** *31*: 5595).

Formulations

Compounds of the invention are administered orally in a total daily dose of about 0.1 mg/kg/dose to about 100 mg/kg/dose, preferably from about 0.3 mg/kg/dose to about 30 mg/kg/dose. The most preferred dose range is from 0.5 to 10 mg/kg (approximately 1 to 20 nmoles/kg/dose). The use of time-release preparations to control the rate of release of the active ingredient may be preferred. The dose may be administered in as many divided doses as is convenient. When other methods are used (e.g. intravenous administration), compounds are administered to the affected tissue at a rate from 0.3 to 300 nmol/kg/min, preferably from 3 to 100 nmoles/kg/min. Such rates are easily maintained when these compounds are intravenously administered as discussed below.

For the purposes of this invention, the compounds may be administered by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters. Oral administration is generally preferred.

Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in

order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to

provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain 20 to 2000 μmol (approximately 10 to 1000 mg) of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions. It is preferred that the pharmaceutical composition be prepared which provides easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion should contain from about 0.05 to about 50 μmol (approximately 0.025 to 25 mg) of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

As noted above, formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free flowing form such as a powder or granules, optionally mixed with a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropyl methylcellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach. This is particularly advantageous with the compounds of formula 1 when such compounds are susceptible to acid hydrolysis.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, or an appropriate fraction thereof, of a fructose 1,6-bisphosphatase inhibitor compound.

It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art.

Utility

FBPase inhibitors at the AMP site may be used to treat diabetes mellitus, lower blood glucose levels, and inhibit gluconeogenesis.

FBPase inhibitors at the AMP site may also be used to treat excess glycogen storage diseases. Excessive hepatic glycogen stores are found in patients with some glycogen storage diseases. Since the indirect pathway contributes significantly to glycogen synthesis (Shulman, G.I. Phys. Rev. 72:1019-1035 (1992)), inhibition of the indirect pathway (gluconeogenesis flux) is expected to decrease glycogen overproduction.

FBPase inhibitors at the AMP site may also be used to treat or prevent diseases associated with increased insulin levels. Increased insulin levels are associated with an increased risk of cardiovascular complications and atherosclerosis (Folsom, et al., Stroke, 25:66-73 (1994); Howard, G. et al., Circulation 93:1809-1817 (1996)). FBPase inhibitors are expected to decrease postprandial glucose levels by enhancing hepatic glucose uptake. This effect is postulated to occur in individuals that are non-diabetic (or pre-diabetic, i.e. without elevated HGO or fasting blood glucose levels). Increased hepatic glucose uptake will decrease insulin secretion and thereby decrease the risk of diseases or complications that arise from elevated insulin levels.

The compounds of this invention and their preparation can be understood further by the examples which illustrate some of the processes by which these compounds are prepared. These examples should not however be construed as specifically limiting the invention and variations of the invention, now known or later developed, are considered to fall within the scope of the present invention as hereinafter claimed.

EXAMPLES

Example 1.

Preparation of 2-Furaldehyde-5-diethylphosphonate

Method A:

To a solution of 25 mL (147.5 mmol) 2-furaldehyde diethyl acetal in 25 ml of THF at -78 °C, was added 96 mL (147.2 mmol) of a 1.6 M BuLi hexane solution. The solution was allowed to stir for 1 h at -78 °C and 24 mL (166.1 mmol) chlorodiethylphosphonate was added and stirred for 0.5 h. The mixture was quenched at -78 °C with a saturated NH_4Cl solution. The precipitates formed were filtered and the filtrate concentrated. The mixture was partitioned

between water and CH_2Cl_2 and separated. The organic layer was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting brown oil was treated with 80% acetic acid and heated at 90 °C for 4 h. Chromatography on silica using 75% ethyl acetate/hexanes yielded 9.1 g (39.2 mmol, 26.6%) of a clear oil.

Method B:

To a solution of 2.8 mL (13.75 mmol) TMEDA and 1.0 mL (13.75 mmol) furan in 9 mL of diethyl ether at -78 °C, was added 8.6 mL (13.75 mmol) of a 1.6 M BuLi hexane solution. The solution was allowed to stir for 0.5 hour at -78 °C and 2.19 mL (15.25 mmol) chlorodiethylphosphonate was added and stirred for 2 h. The mixture was quenched at -78 °C with a saturated sodium bicarbonate solution. The mixture was partitioned between water and CH_2Cl_2 and separated. The organic layer was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting brown oil was purified through Kugelrohr distillation yielding 1.978 g (9.696 mmol, 70.5%) of a clear oil.

To a solution of 16.01 g (78.41 mmol) 2-diethylphosphonfuran in 400 mL of tetrahydrofuran at -78 °C, was added 58.81 mL (117.62 mmol) of a 2M LDA solution. The solution was allowed to stir for 0.3 h at -78 °C and 9.67 mL (156.82 mmol) methylchloroformate was added and stirred for 0.5 h. The mixture was quenched at -78 °C with a saturated sodium bicarbonate solution. The mixture was partitioned between water and CH_2Cl_2 and separated. The organic layer was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting oil was purified by silica gel chromatography yielding 5.6 g (18.2 mmol, 31%) of a clear yellow oil.

Method C:

To a solution of 168 g (1.75 mol) 2-furaldehyde in 500 mL toluene was added 215 mL (1.75 mol) of N,N'-dimethylethylene diamine. The solution was refluxed using a Dean Stark trap to remove H_2O. After 2 hours of reflux, the solvent was removed under reduced pressure. The resulting dark mixture was vacuum distilled (3 mm Hg) and the fraction at 59-61 °C was collected yielding 247.8 g (85%) of clear, colorless oil.

A solution of 33.25 g (0.2 mol) furan-2-(N,N'-dimethylimidazolidine) and 30.2 mL (0.2 mol) tetramethylethylenediamine in 125 mL THF was cooled in a dry ice/IPA bath. A solution of 112 mL n-BuLi in hexane(0.28 mol,2.5M) was

added dropwise, maintaining temperature between -50 and -40 °C during addition. The reaction was allowed to warm to 0 °C over 30 minutes and was maintained at 0 °C for 45 minutes. The reaction was then cooled in a dry ice/IPA bath to -55 °C. This cooled solution was transferred to a solution of 34.7 mL (0.24 mol) diethylchlorophosphate in 125 mL THF and cooled in a dry ice/IPA bath over 45 minutes maintaining the reaction temperature between -50 °C and -38 °C. The reaction was stirred at room temperature overnight. The reaction mixture was evaporated under reduced pressure. Ethyl acetate and H_2O were added to the residue and the layers separated. The H_2O layer was washed with ethyl acetate. The ethyl acetate layers were combined, dried over magnesium sulfate and evaporated under reduced pressure yielding 59.6 g (98%) of a brown oil.

To a solution of 59.6 g 5-diethylphosphonofuran-2-(N,N'-dimethylimidazolidine) in 30 mL H_2O was added 11.5 mL of conc. H_2SO_4 dropwise until pH = 1 was obtained. The aqueous reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated sodium bicarbonate, dried over magnesium sulfate and evaporated to a brown oil. The brown oil was added to a silica column and was eluted with hexane/ethyl acetate. Product fractions were pooled and evaporated under reduced pressure yielding a dark yellow oil, 28.2 g (62%).

Example 2:
Preparation of 5-diethylphosphono-2-thiophenecarboxaldehyde.
Step 1.

A solution of 1.0 mmol 2-thienyl lithium in THF was treated with 1.0 mmol diethyl chlorophosphate at -78 °C for 1 h. Extraction and chromatography gave diethyl 2-thiophenephosphonate as a clear oil.

Step 2.

A solution 1.0 mmol of diethyl 2-thiophenephosphonate in tetrahydrofuran was treated with 1.12 mmol LDA at -78 °C for 20 min. 1.5 mmol methyl formate was added and the reaction was stirred for 1 hr. Extraction and chromotagraphy gave 5-diethylphosphono-2-thiophenecarboxaldehyde as a clear yellow oil.

Example 3:

General methods for the preparation of substituted 1,2-phenylenediamines

Method A:

Step 1.

Bromination of nitroanilines.

To a solution of 1.0 mmol of sustituted nitroaniline in 10 mL of $CHCl_3$ or a mixture of $CHCl_3$ and MeOH (7:1) was added a solution containing one equivalent of Br_2 in 5 mL of $CHCl_3$ over a period of 30 min. After stirring for 2 days at room temperature, extractive isolation provided the bromination product.

Step 2.

Reduction of nitroanilines

To a solution of 1.0 mmol of substituted nitroaniline in 15 mL of MeOH was added 15mL of saturated solution of sodium dithionite. Filtration followed by removal of solvent and extraction with EtOAc provided the pure diamine.

Step 3.

Preparation of 2,1,3-benzoselenadiazole.

To a solution of 1.0 mmol of substituted diamine in 3 mL of 50% aq. ethanol was added a solution of 1.0 mmol of SeO_2 in 1.5 mL of H_2O. The mixture quickly thickened to a slurry. The solid separated out, was filtered, washed with water, and dried.

Step 4.

Nitration of benzoselenadiazoles

To a cold (0 °C) suspension of 1.0 mmol of substituted 2,1,3-benzoselenadiazole was added dropwise a solution of 2.0 mmol of HNO_3 in 1 mL of H_2SO_4. The resultant suspension was stirred for 2 h at 15° C. The dark solution was poured onto ice, filtered, washed with water, and dried.

In the case of 5-fluoro-7-bromo-2,1,3-benzoselenadiazole there were two products in 2:1 ratio, major being the required compound, 4-nitro-5-fluoro-7-bromo-2,1,3-benzoselenadiazole. This was extracted with hot toluene from the byproduct, 4-nitro-5-hydroxy-7-bromo-2,1,3-benzoselenadiazole.

Step 5.

Substituted 3-nitro-1,2-phenylenediamine preparation

A mixture of 1.0 mmol of substituted 4-nitro-2,1,3-benzoselenadiazole in 3 mL of 57% HI was stirred at room temperature for 2 h. Saturated $NaHSO_3$ was

added and the mixture was neutralized with concentrated NH_3 solution. The product was extracted with $CHCl_3$ (5x10 mL) and the extracts were washed, dried, and evaporated.

Method B:

From 2-nitrohalobenzenes:

To a solution of 20 mmol of substituted 2-halonitrobenzene in 70 mL of DMF was added 35 mmol of alkyl or arylamine at 0 °C. After 0.5 h TLC (ethyl acetate/hexane 2:1) indicated the completion of reaction. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried, and evaporated to yield the displacement products.

Method C:

From 2-nitroanilines:

To a solution of 10 mmol of substituted 2-nitroaniline, 20 mmol of alkyl or arylaldehyde, and 60 mmol of acetic acid in 30 mL of 1,2-dichloroethane was added 30 mmol sodium triacetoxyborohydride at 0°C. The reaction was stirred overnight under nitrogen atmosphere and was quenched with saturated sodium bicarbonate solution. The product was extracted with EtOAc (3 x 75 mL) and the extract was washed, dried and evaporated. The residue was chromatographed on a silica gel column eluting with hexane-ethyl acetate (3:1) to yield the product.

These nitroanilines can be reduced to 1,2-phenylenediamines by the procedure given in the Example 3, Method A, Step 2.

Example 4.

Preparation of 2-substituted benzimidazole.

Method A:

Step 1.

A mixture of 1.0 mmol of sustituted 1,2-phenylenediamine and 1.0 mmol of 2-furaldehyde-5-diethylphosphonate in 10 mL of toluene was refluxed (oil bath temp. 140-150°C) for 1-16 h with a Dean Stark trap to remove water. Solvent was removed under reduced pressure and used the product for the next step without further purification.

Step 2.

A solution of 1.0 mmol of this coupled product and 1.0 mmol of I_2 in 5 mL of ethanol was stirred at room temperature for 1-16 h. Extraction and chromatography provided the title compound as an orange solid.

Method B:

To a solution of 1.0 mmol of substituted 1,2-phenylenediamine and 1.0 mmol of 2-furaldehyde-5-diethylphosphonate in 3 mL of DMF was added 0.2-2.0 mmol of $FeCl_3$ and heated for 1-7 h at 90 °C while bubbling air through the solution. Extraction and chromatography provided the condensation product as an orange solid.

Method C:

A solution of 1.0 mmol of substituted 1,2-phenylenediamine and 1.0 mmol of 2-furaldehyde-5-diethylphosphonate in 2 mL of MeOH and AcOH mixture (3:1) was stirred at room temperature for 16 h. Extraction and chromatography provided the condensation product as a solid.

Method D:

A mixture of 1.0 mmol of sustituted 1,2-phenylenediamine and 1.5 mmol of diethylphosphomethyl acetaldehyde dimethyl acetal ether in 4 mL of THF was heated at 75° C for 40 min. in presence of 0.5 mL of 10% H_2SO_4. Solvent was removed under reduced pressure and used for the next step without further purification.

A solution of 1.0 mmol of this coupled product and 1.0 mmol of I_2 in 5 mL of ethanol was stirred at room temperature for 16 h. Extraction and chromatography provided the required product.

Example 5.

General procedures for alkylation

Method A:

A suspension of 1.5 mmol cesium carbonate, 1.0 mmol of substituted benzimidazole-2-(5-diethylphosphonate)furan and 1.0 mmol of electrophile in 5 mL of dry DMF was heated at 80° C for 1-16 h. Extraction and chromatography provided the alkylation product as a yellow solid.

Method B:(Mitsunobu Reaction)

To a suspension of 2.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole, 6.0 mmol electrophile, 6.0 mmol triphenylphosphine, 5.0 mL diisopropylethylamine and 200 mg 4A molecular sieves in 10 mL of dry CH_3CN was added 12.0 mmol diethyl azodicarboxylate at

0 °C. The solution was allowed to warm to room temperature and stirred overnight. Extraction and chromatography provided the alkylation product as a yellow solid.

Example 6:

General procedures for Pd coupling:

Method A:

A mixture of 1.0 mmol of bromo substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole compound, 2.0 mmol of vinyltributyltin or allyltributyltin, and 0.1 mmol of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ in 4 mL of DMF was stirred and heated at 90° C for 1-16 h. Extraction and chromatography provided the coupled compound.

Method B:

A mixture of 1.0 mmol of bromo substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole, 2.0 mmol of propargyl alcohol or any terminal acetylenic compound, 0.1 mmol of $Pd(PPh_3)_2Cl_2$, and 0.1 mmol of CuI in 1 mL of Et_3N and 10 mL of CH_3CN was stirred and heated at 50-80° C for 1-16 h. Extraction and chromatography provided the coupled compound.

Method C:

A mixture of 1.0 mmol of bromo substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole, 5.0 mmol of substituted phenylboronic acid, 0.1 mmol of $Pd(PPh_3)_4$, 5 mL of sat. Na_2CO_3 and 2 mL of EtOH in 10 mL of diglyme was stirred and heated at 80-90° C for 1-16 h. Extraction and chromatography provided the coupled compound.

The compounds thus obtained can be modified as needed. For example vinyl or propargyl alcohol derivatives can be hydrogenated (see Example 9, Method A) to give the ethyl or propyl alcohol derivatives respectively. These alcohol can be further modified as required *via* alkyl halides (see Example 8) or alkyl sulfonates etc. to number of substituted alkyl compounds by subjecting them to nucleophilic substitution reactions (March, *Advanced Organic Chemistry* , Wiley-Interscience, Fourth Edition, **1992**, 293-500). See Example 7 for the cyclopropanation of the vinyl derivative.

Example 7.

Cyclopropynation of the 4-nitro-7-vinyl-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole.

To a suspension of 1.0 mmol of 4-nitro-7-vinyl-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole and 0.1 mmol of $Pd(OAc)_2$ in 8 mL of ether was added an ether solution of diazomethane (generated from 3.0 g of 1-methyl-3-nitro-1-nitrosoguanidine) at 0 °C. After stirring at room temperature 20 h solvent was removed and the residue chromatographed to give 4-nitro-7-cyclopropyl-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole.

Example 8.

Halogenation of the 4-amino-7-(4-hydroxybutyl)-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole.

To a cold (0 °C) solution of 1.0 mmol of 4-amino-7-(4-hydroxybutyl)-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole in 20 mL of CH_2Cl_2 was added 3.0 mmol of PPh_3 and 3.0 mmol of CBr_4. After 40 min. at room temperature solvent was removed and the residue was subjected to chromatography to give 4-amino-7-(4-bromobutyl)-5-fluoro-1-isobutyl-2-(2-diethylphosphono-5-furanyl)benzimidazole. CCl_4 gave the corrosponding chloro compound.

Example 9:

General procedures for reduction:

Method A:

A mixture of 1.0 mmol of alkylation product and 20 mg of 10 % Pd/C in 5 mL of DMF or MeOH was hydrogenated using H_2 from a balloon for 0.5-16 h. The reaction mixture was filtered through Celite and chromatographed to provide the reduction product as an oil.

Method B:

To a solution of 1.0 mmol of substituted nitroaniline in 15 mL of MeOH was added 15 mL of a saturated solution of sodium dithionite. Filtration followed by removal of solvent and extraction with EtOAc or $CHCl_3$ provided the pure diamine.

These primary aromatic amines can also be modified as needed. For example N-acetyl derivetives can be prepared by treatment with acetyl chloride or acetic anhydride in presence of a base such as pyridine and mono-, or di-

alkylamines can be synthesized by direct alkylation (see Example 5) or by reductive alkylation (see Example 3, Method C.).

Example 10.

Bromination of 4-amino-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole.

A mixture of 1.0 mmol of 4-amino-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole, and 1.0 mmol of NBS in 5 mL of CCl_4 was stirred at room temperature for 4 h. The mixture was processed by filtration and chromatography to provide o-bromo (21%, R_f= 0.14), p-bromo (25%, R_f= 0.01) and dibromo (36%, R_f= 0.23).

When Br_2 was used in place of NBS, the dibromo compound was formed exclusively. The same procedures were followed for chlorination.

General procedures for phosphonate hydrolysis:

Example 11:

BBr_3 hydrolysis:

To a solution of 1.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole in 3 mL of anhydrous CH_2Cl_2 was added 10 mmol of 1.0 M BBr_3 solution in CH_2Cl_2 at -78°C and the mixture was allowed to warm to room temperature. After 16 h, solvent and excess BBr_3 were removed under reduced pressure and the residue was taken into 3 mL of water. The precipitate was filtered, washed with water, and MeOH and was dried under vaccum at 50° C.

The following compound was prepared in this manner:

11.1: 4-Amino-5-hydroxy-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 206-209 °C; Anal. Cald. for $C_{15}H_{18}N_3O_5P$ + $2.7H_2O$: C: 45.05; H: 5.90; N: 10.51. Found: C: 44.96; H: 5.78; N: 10.14.

Example 12:

TMSBr hydrolysis:

To a solution of 1.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole in 5 mL of anhydrous CH_2Cl_2 was added 10.0 mmol TMSBr at 0 °C. After 16 h stirring at room temperature the solvent and excess TMSBr were removed under reduced pressure. The residue was taken into 15 mL of a 1/5 mixture of acetone/water and was stirred

for 16 h at room temperature. The resulting solid was filtered, washed with water, EtOAc, and MeOH and was dried under vacuum at 50°C.

The following compounds were prepared in this manner:

12.1: 4-Amino-1-ethyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >250 °C; Anal. Cald. for $C_{13}H_{14}N_3O_4P$ + 1 H_2O: C: 48.01; H: 4.96; N: 12.92. Found: C: 48.46; H: 4.79; N: 12.6.

12.2: 4-Amino-1-cyclohexylethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >250 °C; Anal. Cald. for $C_{19}H_{24}N_3O_4P$ + 0.5 H_2O: C: 57.28; H: 6.32; N: 10.55. Found: C: 57.04; H: 5.77; N: 10.32.

12.3: 4-Amino-2-[2-(5-phosphono)furanyl]benzimidazole. mp >240 °C ; Anal. Cald. for $C_{11}H_{10}N_3O_4P$ + $2H_2O$: C: 41.91; H: 4.48; N: 13.33. Found: C: 41.52; H: 4.34; N: 13.09.

12.4: 4-Amino-1-methyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >230 °C ; Anal. Cald. for $C_{12}H_{12}N_3O_4P$ + 1 H_2O: C: 46.31; H: 4.53; N: 13.50. Found: C: 46.52; H: 4.31; N: 13.37.

12.5: 4-Amino-1-(4-methylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole acetic acid salt. mp = 222-225 °C ; Anal. Cald. for $C_{19}H_{18}N_3O_4P$ + AcOH $0.25H_2O$: C: 56.31; H: 5.06; N: 9.38. Found: C: 56.50; H: 5.23; N: 9.63.

12.6: 4-Amino-1-(3-carbomethoxybenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 198-202 °C ; Anal. Cald. for $C_{20}H_{18}N_3O_6P$: C: 55.55; H: 4.39; N: 9.63. Found: C: 55.12; H: 4.29; N: 9.18.

12.7: 4-Amino-1-isobutyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp = 195-200 °C ; Anal. Cald. for $C_{15}H_{18}N_3O_4P$ +1.5 H_2O: C: 49.73 ; H: 5.84; N: 11.60. Found: C: 50.08; H: 5.51; N: 11.23.

12.8: 4-Amino-1-ethylbenzimidazol-2-yl-methyleneoxymethyl phosphonic acid. mp = 208-210 °C ; Anal. Cald. for $C_{11}H_{16}N_3O_4P$ + $2.5H_2O$: C: 40.00; H: 6.41; N: 12.72. Found: C: 40.14; H: 5.17; N: 12.37. >88% pure by HPLC.

12.9: 4-Amino-1-(3-methylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp>250 °C ; Anal. Cald. for $C_{19}H_{18}N_3O_4P$ + H_2O: C: 56.86; H: 5.02; N: 10.47. Found: C: 56.66; H: 4.59; N: 10.34.

12.10: 4-Amino-1-[2'-(3"-carboethoxy-5",6",7",8"-tetrahydronaphthyl)ethyl]-2-[2-(5-phosphono)furanyl]benzimidazole. mp 198-202 °C ; Anal. Cald. for $C_{26}H_{28}N_3O_6P$ + H_2O: C: 59.20; H: 5.73; N: 7.97. Found: C: 59.23; H: 5.54; N: 7.68.

12.11: 4-Amino-1-[2'-(3"-carboxy-5",6",7",8"-tetrahydronaphthyl)ethyl]-2-[2-(5-phosphono)furanyl]benzimidazole. mp = 220-224 °C ; Anal. Cald. for

$C_{24}H_{24}N_3O_6P + 2H_2O$: C: 55.71; H: 5.45; N: 8.12. Found: C: 56.18; H: 5.17; N: 7.97.

12.12: 4-Amino-1-propyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >230 °C ; Anal. Cald. for $C_{14}H_{16}N_3O_4P + 1.25\ H_2O$: C: 48.91; H: 5.42; N: 12.22. Found: C: 48.88; H: 5.07; N: 12.26.

12.13: 4-Amino-1-norbornylmethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{19}H_{22}N_3O_4P + 0.75H_2O$: C: 56.93; H: 5.91; N: 10.48. Found: C: 56.97; H: 5.63; N:10.28.

12.14: 4-Amino-1-(3-carboxybenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >250 °C ; Anal. Cald. for $C_{19}H_{16}N_3O_6P + 2.5H_2O$: C: 49.79; H: 4.62; N: 9.17. Found: C: 49.30; H: 4.00; N: 8.49. Mass. cald. for $C_{19}H_{16}N_3O_6P$: 413. Found: $MH^+ = 414$: $MH^- = 412$.

12.15: 4-Amino-1-cyclopentanemethyl-2-[2-(5-phosphono)furanyl]-benzimidazole. mp >230 °C; Anal. Cald. for $C_{17}H_{20}N_3O_4P + 1.4H_2O$: C: 52.82; H: 5.92; N: 10.87. Found: C: 52.81; H: 5.71; N: 10.51.

12.16: 4-Amino-1-cyclopropanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{15}H_{16}N_3O_4P + 0.75\ CH_2Cl_2$: C: 47.65; H: 4.44; N: 10.58. Found: C: 47.81; H: 4.57; N: 10.77.

12.17: 4-Amino-1-cyclobutanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{16}H_{18}N_3O_4P + 0.5\ H_2O$: C: 53.93; H: 5.37; N: 11.79. Found: C: 53.89; H: 5.12; N: 11.48.

12.18: 4-Amino-1-(3-methyl-6,6-dimethyl-2-cyclohexenylmethyl)-2-[2-(5-phosphono)furanyl]benzimidazole. mp >220 °C ; Anal. Cald. for $C_{21}H_{24}N_3O_4PNa_2 + 2\ H_2O$: C: 50.91; H: 5.70; N: 8.48. Found: C: 50.82; H: 5.53; N: 8.26.

12.19: 4-Amino-1-(2-methyl-2-butenyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 190-195 °C ; Anal. Cald. for $C_{16}H_{18}N_3O_4P + 1.5H_2O$: C: 51.34; H: 5.65; N: 11.23. Found: C: 51.68; H: 5.59; N: 11.37.

12.20: 4-Amino-1-[(1S,2S,5S)myrtanyl]-2-[2-(5-phosphono)furanyl] benzimidazole. mp>200 °C ; Anal. Cald. for $C_{21}H_{26}N_3O_4P + 1H_2O$: C: 58.19; H: 6.51; N: 9.69. Found: C: 58.49; H: 6.12; N: 9.65.

12.21: 4-Amino-1-(4-t-butylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 246-249 °C ; Anal. Cald. for $C_{22}H_{21}N_3O_4P + 0.66H_2O$: C: 60.40; H: 5.84; N: 9.60. Found: C: 60.37; H: 5.45; N: 8.87.Mass. cald. for $C_{22}H_{21}N_3O_4P = 425$. Found: $MH^+ = 426$; $MH^- = 424$.

12.22: 4-Amino-1-(4-cyclohexyl-1-butyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >230 °C ; Anal. Cald. for $C_{21}H_{28}N_3O_4P$ + 0.6H_2O: C: 58.90; H: 6.87; N: 9.81. Found: C: 58.67; H: 6.54; N: 9.46.

12.23: 4-Amino-1-(3-cyclohexyl-1-propyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >218 °C ; Anal. Cald. for $C_{20}H_{26}N_3O_4P$ + 1.2 H_2O: C: 56.52; H: 6.73; N: 9.89. Found: C: 56.71; H: 6.30; N: 9.47.

12.24: 4-Amino-1-(3-carboxypropyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >225 °C ; Anal. Cald. for $C_{15}H_{16}N_3O_6P$: C: 49.3; H: 4.42; N: 11.51. Found: C: 49.01; H: 4.22; N: 11.21.

12.25: 4-Amino-1-(3-carboethoxypropyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >225 °C; Anal. Cald. for $C_{17}H_{20}N_3O_6P$: C: 51.89; H: 5.13; N: 10.69. Found: C: 51.68; H: 5.08; N: 10.34.

12.26: 4-Amino-1-(t-butylmethylketone)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >225 °C ; Anal. Cald. for $C_{17}H_{20}N_3O_5P$ + 1.3 H_2O: C: 50.95; H: 5.68; N: 10.49. Found: C: 50.83; H: 5.21; N: 9.85.

12.27: 4-Amino-1-cycloheptanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp 198 °C ; Anal. Cald. for $C_{19}H_{24}N_3O_4P$ + 0.5 H_2O: C: 57.27; H: 6.25; N: 10.02. Found: C: 57.46; H: 6.22; N: 9.86.

12.28: 4-Amino-1-cyclohexanemethyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp 210 °C ; Anal. Cald. for $C_{18}H_{22}N_3O_4P$ + 0.5 AcOH: C: 56.29; H: 5.97; N: 10.37. Found: C: 56.00; H: 5.96; N: 10.32.

12.29: 4-Amino-1-benzyl-2-[2-(5-phosphono)furanyl]benzimidazole. mp >250 °C ; Anal. Cald. for $C_{18}H_{14}N_3O_4PNa_2$ + 1.6H_2O: C: 48.78; H: 3.94; N: 9.48. Found: C: 49.10; H: 4.11; N: 8.73. Mass. cald. for $C_{18}H_{16}N_3O_4P$ = 369. Found: MH^+ = 370; MH^- = 368.

12.30: 4-Amino-1-(3-trifluoromethylbenzyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp 235-239 °C ; Anal. Cald. for $C_{19}H_{15}N_3O_4PF_3$ +0.1 H_2O +1.6CH_3CO_2H: C: 49.82; H: 4.07; N: 7.85. Found: C: 50.31; H: 4.04; N: 7.38.

12.31: 4-Amino-1-(3-carbamoylpropyl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >225 °C ; Anal. Cald. for $C_{15}H_{17}N_4O_5P$: C: 49.44; H: 4.71; N: 15.38. Found: C: 49.00; H: 5.47; N: 14.06. Mass. cald. for $C_{15}H_{17}N_4O_5P$ = 364; MH^+ = 365: MH^- = 363.

12.32: 4-Amino-1-(7-hydroxy-3R,7-dimethyloctyl)-2-[2-(5-phosphono)furanyl]benzimidazole. mp >250 °C ; Anal. Cald. for $C_{21}H_{28}N_3O_5PNa_2$ + 1.5 H_2O: C: 49.80; H: 6.17; N: 8.30. Found: C: 49.43; H: 6.01; N: 8.10.

12.33: 4-Amino-1-(4-chlorobutyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >240 °C ; Anal. Cald. for $C_{15}H_{17}N_3O_4ClP + 0.5\ H_2O$: C: 47.57; H: 4.79; N: 11.09. Found: C: 47.62; H: 4.57; N: 10.87.

12.34: 4-Amino-1-(4-phenylbenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >220 °C ; Anal. Cald. for $C_{24}H_{20}N_3O_4P + 0.66\ H_2O$: C: 63.01; H: 4.70; N: 9.19. Found: C: 63.09; H: 4.50; N: 8.81.

12.35: 4-Amino-1-(3-chloropropyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>250 °C ; Anal. Cald. for $C_{14}H_{15}N_3O_4ClP + 0.7\ H_2O$: C: 44.83; H: 4.61; N: 10.37. Found: C:44.50; H:4.29; N:10.96.

12.36: 4-Amino-1-(4-hydroxybutyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>250 °C ; Anal. Cald. for $C_{15}H_{16}N_3O_5PNa_2 + 1.8\ H_2O$: C: 41.68; H: 4.71; N: 9.04. Found: C: 41.29; H: 4.60; N: 9.31.

12.37: 4-Amino-1-(3-furanylmethyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>230 °C ; Mass. Cald. 358; Obs. 358.

12.38: 4-Amino-1-(3-hydroxybenzyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp 232-4 °C ; Anal. Cald. for $C_{18}H_{16}N_3O_5P + 2\ H_2O$: C: 51.31; H: 4.78; N: 9.97. Found: C: 51.01; H: 4.72; N: 10.15.

12.39: 4-Amino-1-[(2-methoxy)phenethyl]-2-[2-(5-phosphono)furanyl] benzimidazole. mp >240 °C ; Anal. Cald. for $C_{20}H_{20}N_3O_5P + 1\ H_2O$: C: 55.69; H: 5.14; N: 9.64. Found: C: 55.2; H: 4.90; N: 9.35.

12.40: 4-Amino-1-[(3-methoxy)phenethyl]-2-[2-(5-phosphono)furanyl] benzimidazole. mp >240 °C ; Anal. Cald. for $C_{20}H_{20}N_3O_5P + 1\ H_2O$: C: 55.69; H: 5.14; N: 9.64. Found: C: 55.09; H: 4.71; N: 9.52.

12.41: 4-Amino-1-(3-thienylmethyl)-2-[2-(5-phosphono)furanyl] benzimidazole. mp = 200-205 °C ; Anal. Cald. for $C_{16}H_{14}N_3O_4PS + 1.7\ H_2O$: C: 47.34; H: 4.32; N: 10.35. Found: C: 46.90; H: 3.88; N: 10.05.

12.42: 4-Amino-5,7-dibromo-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >215 °C ; Anal. Cald. for $C_{15}H_{16}Br_2N_3O_4P$: C:36.54; H: 3.27; N: 8.52. Found: C: 36.55; H: 3.22; N: 8.13.

12.43: 4-Amino-1-(1-hydroxyprop-3-yl)-2-[2-(5-phosphono) furanyl]benzimidazole. mp >213 °C ;.Mass. Cald. 336; Obs. 336.

12.44: 4-Amino-5-bromo-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >239 °C ; Anal. Cald. for $C_{15}H_{17}N_3O_4BrP + 0.5\ H_2O$: C: 42.57; H: 4.29; N: 9.93. Found: C: 42.44; H: 3.99; N: 9.69.

12.45: 4-Amino-1-ethyl-2-[1-(2-phosphonomethyloxy)phenyl] benzimidazole. mp 180-185 °C ; Anal. Cald. for $C_{16}H_{18}N_3O_4P$ + 0.8 H_2O: C: 53.13; H: 5.46; N: 11.62. Found: C: 52.98; H: 5.20; N: 11.32.

12.46: 4-Amino-7-bromo-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >230 °C ; Anal. Cald. for $C_{15}H_{17}N_3O_4BrP$ + 0.25 H_2O: C: 43.03; H: 4.21; N: 10.04. Found: C: 42.69; H:3.87; N: 9.63.

12.47: 4-Amino-7-bromo-1-cyclobutanemethyl-2-[2-(5-phosphono) furanyl]benzimidazole. mp >200 °C ; Anal. Cald. for $C_{16}H_{17}BrN_3O_4P$ + H_2O + 0.06 EtOAc: C: 43.24; H: 4.33; N: 9.38. Found: C: 43.40; H: 3.95; N: 9.11.

12.48: 4-Amino-5-bromo-1-cyclobutanemethyl-2-[2-(5-phosphono) furanyl]benzimidazole. mp >200 °C ; >91% pure by HPLC.

12.49: 4-Amino-5-chloro-1-isobutyl-2-[2-(5-phosphono)furanyl] benzimidazole. mp >>240 °C ; Anal. Cald. for $C_{15}H_{17}ClN_3O_4P$ + 0.8H_2O: C: 46.90; H: 4.88; N: 10.94. Found: C: 46.99; H: 4.53; N: 10.76.

12.50: 4-Amino-5,7-dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 205-207 °C; Anal.Cald. for $C_{15}H_{16}N_3O_4Cl_2P$ + 0.5H_2O: C: 43.60; H: 4.15; N: 10.17. Found: C: 43.64; H: 4.03; N: 10.02.

12.51: 4-Amino-1-(2-thienylethyl)-2-[2-(5-phosphono)furanyl benzimidazole. mp = 225 °C; Anal. Cald. for $C_{17}H_{16}N_3O_4PS$+1.1H_2O. C: 50.12; H: 4.45 N: 10.31. Found: C: 49.67; H: 3.96; N: 10.45.

12.52: 4-Amino-5-ethyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 220-225 °C; Anal. Cald. for C: 51.34; H: 5.95; N: 10.21.

12.53: 4-Amino-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 230-235 °C; Anal. Cald. for $C_{15}H_{17}N_3O_4PF$ + 0.8 H_2O; C: 49.00; H: 5.10; N: 11.43. Found: C: 49.13; H: 4.81; N: 11.13.

12.54: 4-Amino-5-fluoro-7-chloro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 220-225 °C; Anal. Cald. for $C_{15}H_{16}N_3O_4FClP$ + 0.9 HBr; C: 12; H: 3.70; N: 9.12. Found: C: 39.15; H: 3.46; N: 8.77.

12.55: 4-Amino-5-methoxy-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 212-213 °C; Anal. Cald. for $C_{16}H_{20}N_3O_5P$+H_2O: C: 50.13; H: 5.78; N: 10.96. Found: C: 49.93; H: 5.55; N: 10.79.

12.56: 4-Amino-2-[2-(5-phosphono)furanyl]-1-[(3-amino)phenethyl] benzimidazole. mp = 297 °C; Anal. Cald. for $C_{19}H_{19}N_4O_4P$ + 0.4 AcOH + 0.1 MeCN + 1.5 H_2O: C: 52.97; H: 5.31; N: 12.66. Found: C: 52.83; H: 5.17; N: 11.99. Found: C: 52.65; H: 4.92; N: 12.14.

12.57: 4-Amino-1-[(2-ethyl)pentyl]benzimidazol-2-yl-methylenoxymethyl phosphonic acid. mp = 85 °C; Anal. Cald. for $C_{15}H_{24}N_3O_4P$ + 1/2 H_2O + 2 HBr + 1/3 toluene: C: 38.05; H: 5.49; N: 7.78. Found: C: 38.30; H: 5.45; N: 7.34.

12.58: 4-Amino-5-bromo-6,7-dichloro-2-(2-phosphono-5-furanyl) benzimidazole. mp = 224-225 °C; Anal. Cald. for : C: 38.92; H: 3.23; N: 5.92

12.59: 5-Amino-2-(2-Phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_{10}N_3PO_4$ + CF_3CO_2H + 1.5 H_2O: C: 37.16; H: 3.36; N: 10.00. Found: C: 37.40; H: 3.31; N: 9.77.

12.60: 4-Amino-5-propyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 207-210 °C; Anal. Cald. for $C_{18}H_{24}N_3PO_4$ + 2 H_2O: C: 52.30; H: 6.83; N: 10.16. Found: C: 52.05; H: 6.71; N: 9.95.

12.61: 4-Amino-5-fluoro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 258- 260 °C; Anal. Cald. for $C_{15}H_{15}N_3O_4P$ F + 0.3 H_2O: C: 50.51; H: 4.41; N: 11.78. Found: C: 50.21; H: 4.28; N: 11.45.

12.62: 4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 195-200 °C; Anal. Cald. for $C_{15}H_{16}N_3BrFPO_4$: C: 41.69; H: 3.73; N: 9.72. Found: C: 41.59; H: 3.81; N: 9.67.

12.63: 4-Amino-5-fluoro-6-chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 175-180 °C; Anal. Cald. for $C_{15}H_{16}N_3ClFPO_4$ + 2.0 H_2O: C: 42.52; H: 4.76; N: 9.92. Found: C: 42.60; H: 4.56; N: 9.81.

12.64: 4-Amino-7-ethyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 245-246 °C; Anal. Cald. for $C_{17}H_{21}N_3O_4FP$ + 0.4 H_2O: C: 52.55; H: 5.66; N: 10.81. Found: C: 52.40; H: 5.79; N: 10.47.

12.65: 7-Amino-4-ethyl-6-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 249-250 °C; Anal. Cald. for $C_{17}H_{21}N_3O_4FP$: C: 53.54; H: 5.55; N: 11.02. Found: C: 53.20; H: 5.38; N: 10.73.

12.66: 4-Amino-7-cyclopropyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 250-255 °C (dec.); Anal. Cald. for $C_{18}H_{21}N_3O_4FP$ + 0.25 H_2O: C: 54.34; H: 5.45; N: 10.56. Found: C: 54.14; H: 5.28; N: 10.31.

12.67: 4-Amino-7-phenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 240-241 °C (dec.); Anal. Cald. for $C_{21}H_{21}N_3O_4FP$ + $0.05H_2O$: C: 58.62; H: 4.94; N: 9.77. Found: C: 58.27; H: 4.86; N: 9.47.

12.68: 4-Amino-7-p-fluorophenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 239-240 °C (dec.); Anal. Cald. for $C_{21}H_{20}N_3O_4F_2P$: C: 56.38; H: 4.51; N: 9.39. Found: C: 56.38; H: 4.36; N: 9.14.

12.69: 4-Amino-7-p-chlorophenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 235-236 °C (dec.); Anal. Cald. for $C_{21}H_{20}N_3O_4FClP$: C: 54.38; H: 4.35; N: 9.06. Found: C: 54.10; H: 4.20; N: 8.73.

12.70: 4-Amino-7-vinyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 238-242 °C; Anal. Cald. for $C_{17}H_{19}N_3O_4FP$ + 1.2 H_2O: C: 50.93; H: 5.38; N: 10.48. Found: C: 51.07; H: 5.37; N: 10.12.

12.71: 4-Amino-7-(4-methylpentane)-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 185-195 °C (dec.); Anal. Cald. for $C_{21}H_{29}N_3O_4FP$+0.25 H_2O: C: 57.07; H: 6.73; N: 9.51. Found: C: 57.03; H: 6.89; N: 9.24.

12.72: 4-Amino-7-(3,3-dimethylbutane)-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 200-205 °C (dec.); Anal. Cald. for $C_{21}H_{29}N_3O_4FP$ + 0.75 H_2O: C: 55.93; H: 6.82; N: 9.32. Found: C: 55.84; H: 6.62; N: 9.15.

12.73: 4-Amino-5-fluoro-1-(2-ethylbutyl)-2-(2-phosphono-5-furanyl)benzimidazole. mp = 178-182 °C (dec.); Anal. Cald. for $C_{17}H_{21}N_3O_4FP$ + 1.0 H_2O: C: 51.13; H: 5.80; N: 10.52. Found: C: 51.03; H: 5.58; N: 10.27.

12.74: 4-Amino-7-m-methoxyphenyl-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 208-212 °C (dec.); Anal. Cald. for $C_{22}H_{23}N_3O_5FP$ + 0.25 H_2O: C: 56.96; H: 5.11; N: 9.06. Found: C: 57.02; H: 5.14; N: 8.52.

12.75: 4-Amino-7-ethyl-5-fluoro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 178-185 °C; Anal. Cald. for $C_{17}H_{19}N_3O_4FP$ + 1.3 H_2O: C: 50.70; H: 5.41; N: 10.43. Found: C: 50.98; H: 5.29; N: 10.05.

12.76: 4-Amino-5-fluoro-1-(3-pentyl)-2-(2-phosphono-5-furanyl)benzimidazole. mp = 180-185 °C (dec.); Anal. Cald. for $C_{16}H_{19}N_3O_4FP$ + 1.5 H_2O: C: 48.73; H: 5.62; N: 10.66. Found: C: 48.60; H: 5.55; N: 10.49.

12.77:5,6,7-Trifluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 250-260 °C; Anal. Cald. for $C_{15}H_{14}N_2O_4F_3P$: C: 48.14; H: 3.77; N: 7.49. Found: C: 48.04; H: 3.81; N: 7.43.

12.78:4,5,6-Trifluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 155-158 °C; Anal. Cald. for $C_{15}H_{14}N_2O_4F_3P$: C: 48.14; H: 3.77; N: 7.49. Found: C: 48.04; H: 3.81; N: 7.43.

12.79: 4-Amino-7-(propane-3-ol)-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 170-173 °C; Anal. Cald. for $C_{18}H_{23}N_3O_5FP$ + 1.0 H_2O: C: 50.35; H: 5.87; N: 9.79. Found: C: 50.31; H: 5.80; N: 9.62.

12.80: 4-Amino-5-fluoro-7-(3-bromopropyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 190-195 °C (dec.); Anal. Cald. for $C_{18}H_{22}N_3O_4FBrP$: C: 45.59; H: 4.68; N: 8.86. Found: C: 45.87; H: 4.87; N: 8.70.

12.81: 4-Amino-5-fluoro-7-n-propyl-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 220-230 °C (dec.); Anal. Cald. for $C_{18}H_{23}N_3O_4FP$ + 0.85 H_2O: C: 52.64; H: 6.06; N: 10.23. Found: C: 53.00; H: 6.09; N: 9.70.

12.82: 4-Amino-5-fluoro-7-(4-bromobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 200-220 °C (dec.); Anal. Cald. for $C_{19}H_{24}N_3O_4FBrP$ + 0.5 H_2O: C: 45.89; H: 5.07; N: 8.45. Found: C: 45.61; H: 5.10; N: 8.20.

12.83: 4-Amino-5-fluoro-7-(4-chlorobutyl)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 210-220 °C (dec.); Anal. Cald. for $C_{19}H_{24}N_3O_4FClP$ + 0.25 H_2O: C: 50.90; H: 5.51; N: 9.37. Found: C: 50.96; H: 5.53; N: 9.13.

12.84: 4-Amino-5-fluoro-7-(3-N,N-dimethylpropylamine)-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole hydrobromide salt. mp = 208-212 °C (dec.); Anal. Cald. for $C_{20}H_{28}N_4O_4FP$ + 1.0 Hbr + 2.0 H_2O: C: 43.25; H: 5.99; N: 10.09. Found: C: 43.39; H: 5.74; N: 9.90.

12.85: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(2-phosphono-5-thionyl)benzimidazole. Anal. Cald. for $C_{17}H_{18}N_2O_3PSCl$: C: 51.45; H: 4.57; N: 7.06; Found: C: 51.28; H: 4.58; N: 6.92.

12.86: 4-Amino-5-fluoro-7-ethyl-1-2(2-phosphono-5-furanyl)benzimidazole. mp = 180-186° C; Anal. Cald. for $C_{13}H_{13}N_3O_4FP$ + 1.2 H_2O: C: 45.02; H: 4.48, N: 12.11. Found: C: 45.17; H: 4.52; N: 11.81.

<u>Example 13:</u>

<u>HBr hydrolysis:</u>

A solution of 1.0 mmol of substituted 2-[(5-diethylphosphonate)furanyl]benzimidazole in 10 ml of 30 % HBr was heated at 80° C for 0.5-3 h. The solvent was removed under reduced pressure and the

residue was taken into 3 ml of water. The solid precipitated was filtered washed with water and dried under vaccum at 50°C.

The following compounds were prepared in this manner:

13.1: 2-(2-Phosphono-5-furanyl)benzimidazole. mp>250 °C ; Anal. Cald. for $C_{11}H_9N_2O_4P$ + 0.55 HBr + H_2O: C: 40.44; H: 3.56; N: 8.57. Found: C: 40.74; H: 3.51; N: 8.53.

13.2: 1-Isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 200-203 °C; Anal. Cald. for $C_{15}H_{17}N_2O_4P$ + 0.75 H_2O: C: 53.97; H: 5.59; N: 8.39. Found: C: 53.70; H: 5.37; N: 8.24.

13.3: 2-[5,6-Indano-1(H)-imidazol-2-yl]furan-5-phosphonic acid. Anal. Cald. for $C_{14}H_{13}N_2PO_4$ + 1.25 H_2O: C: 51.46; H: 4.78; N:.8.57. Found: C: 51.43; H: 4.38; N: 8.44.

13.4: 2-(1-Isobutyl-5,6-indanoimidazol-2-yl)furan-5-phosphonic acid. Anal. Cald. for $C_{18}H_{21}N_2PO_4$ + 0.5 H_2O: C: 58.53; H: 6.00; N: 7.58. Found: C: 58.45; H: 5.62; N: 7.44.

13.5: 2-(1,8-Diaza-1,2,3,4-tetrahydroacenaphthen-9-yl)furan-5-phosphonic acid. Anal. Cald. for $C_{14}H_{13}N_2PO_4$ + 0.5 HBr + 0.5 H_2O: C: 47.54; H: 4.13; N: 7.48. Found: C: 47.33; H: 4.16; N: 7.48.

13.6: 2-(2-Phosphono-5-furanyl)-5-trifluoromethylbenzimidazole. Anal. Cald. for $C_{12}H_8F_3N_2O_4P$ + 1.2 H_2O. C: 40.74; H: 2.96; N: 7.92; F: 16.11. Found: C: 40.49; H: 2.71; N: 7.89; F: 16.50.

13.7: 2-(2-Phosphono-5-furanyl)-5-fluorobenzimidazole. Anal. Cald. for $C_{11}H_8FN_2O_4P$ + 2/3 H_2O. C: 44.93; H: 3.19; N: 9.53; F: 6.46. Found: C: 44.91 H: 3.05; N: 9.34; F: 6.54.

13.8: 2-(2-Phosphono-5-furanyl)-5,6-dichlorobenzimidazole. Anal. Cald. for $C_{11}H_7Cl_2N_2O_4P$ + 0.25 AcOH; C: 39.68; H: 2.32; N: 8.05; Cl: 20.37. Found: C: 39.92; H: 2.28; N: 7.87; Cl: 20.10.

13.9: 2-(2-Phosphono-5-furanyl)-5-chlorobenzimidazole. Anal. Cald. for $C_{11}H_8ClN_2O_4P$ + 0.75 HBr + 0.33 H_2O; C: 36.17; H: 2.60; N: 7.67; Cl: 9.71. Found: C: 36.53; H: 2.43; N: 7.31; Cl: 9.48.

13.10: 2-(2-Phosphono-5-furanyl)-5-methylbenzimidazole. Anal. Cald. for $C_{12}H_{11}N_2PO_4$ + H_2O: C: 48.66; H: 4.42; N: 9.46. Found: C: 48.64; H: 4.20; N: 9.22.

13.11: 2-(2-Phosphono-5-furanyl)-5-(tert-butyl)benzimidazole. Anal. Cald. for $C_{15}H_{17}N_2PO_4$ + H_2O: C: 53.26; H: 5.66; N: 8.28. Found: C: 53.04; H: 5.57; N: 7.96.

13.12: 1-Phenyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 196- 200 °C; Anal. Cald. for $C_{17}H_{13}N_2PO_4$ + 2 H_20 + HBr: C: 44.66; H: 3.97; N: 6.13 . Found: C: 45.06; H: 3.66; N: 6.01.

13.13: 1-(2-Carboxyphenyl)-2-(2-phosphono-5-furanyl)-5-chloro benzimidazole. mp = 220- 224 °C; Anal. Cald. for $C_{18}H_{12}N_2O_6ClP$ + H_2O + 0.2 HBr: C: 47.73; H: 3.16; N: 6.18; Cl: 7.83. Found: C: 48.07; H: 2.86 N: 5.98; Cl: 7.78.

13.14: 5-Nitro-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_8N_3PO_6$ + H_2O: C: 40.38; H: 3.08; N: 12.84. Found: C: 40.28; H: 2.97; N: 12.47.

13.15: 4,5-Dimethyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{13}H_{13}N_2PO_4$ + 0.6 H_2O: C: 51.53; H: 4.72; N: 9.24. Found: C: 51.20; H: 4.64; N: 9.13.

13.16: 5-Chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 238 °C; Anal. Cald. for $C_{15}H_{16}ClN_2O_4P$ + 0.33 HBr; C: 47.23; H: 4.32; N: 7.34; Cl: 9.29. Found: C: 47.37; H: 4.02; N: 6.99; Cl: 9.56.

13.17: 6-Chloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{16}ClN_2O_4P$ + 0.5 HBr: C: 45.59; H: 4.21; N: 7.09; Cl: 8.97. Found: C: 46.02; H: 3.86; N: 7.01; Cl: 8.63.

13.18: 5-Benzophenone-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{18}H_{13}N_2O_5P$ + 1.75 H_2O + .25 HBr: C: 51.47; H: 4.02; N: 6.67. Found: C: 51.63; H: 4.09; N: 6.31.

13.19: 4-Amidinomethyl-2-[2-(5-phosphono)furanyl]-1-[(2-ethyl) pentyl]benzimidazole. mp = 225-230 °C; Anal. Cald. for $C_{19}H_{25}N_4O_4P$ + 0.3 H_2O: C: 55.69; H: 6.30; N: 13.67. Found: C: 55.46; H: 5.77; N: 13.16.

13.20: 1-Isobutyl-4-isobutyloxy-2-(2-phosphono-5-furanyl) benzimidazole. mp = 350 °C; Anal. Cald. for $C_{19}H_{25}N_2O_5P$ + 1.0 H_2O: C: 55.61; H: 6.63; N: 6.83. Found: C: 55.26; H: 6.41; N: 6.59.

13.21: 4-Hydroxy-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 244-245 °C; Anal. Cald. for $C_{15}H_{17}N_2O_5P$ + 1.1 H_2O: C: 50.59; H: 5.43; N: 7.87. Found: C: 50.33; H: 5.38; N: 7.89.

13.22: 5,6-Difluoro-2-(2-Phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7N_2PO_4F_2$ + 0.3 H_20: C: 43.24; H: 2.51; N: 9.17; F: 12.44. Found: C: 43.58; H: 2.63; N: 8.69; F: 12.28.

13.23: 2-(2-Phosphono-5-furanyl)benzimidazole-5-methylcarboxylate. Anal. Cald. for $C_{13}H_{11}N_2O_6P$ + 0.5 H_2O + 0.25 HBr: C: 44.43; H: 3.51; N: 7.97; Found: C: 44.41; H: 3.80; N: 8.16.

13.24: 5,6-Dimethyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{13}H_{13}N_2O_4P$ + 2/3 H_2O: C: 51.34; H: 4.75; N: 9.21. Found: C: 51.48: H: 4.75; N: 8.95.

13.25: 4-Fluoro-1-neopentyl-2-(2-phosphonofuranyl)benzimidazole. Anal. Cald. for $C_{16}H_{18}N_2PO_4F$ + 0.1 H_2O + 0.3 CH_3CO_2H: C: 53.58; H: 5.25; N: 7.53. Found: C: 53.84; H: 5.12; N: 7.05.

13.26: 2-(2-Phosphonofuranyl)-(4,5-benz)benzimidazole. Anal. Cald. for $C_{15}H_{11}N_2PO_4$ + 1.75 H_2O: C: 52.11; H: 4.23; N: 8.10. Found: C: 52.40; H: 4.34; N: 7.70.

13.27: 6-Fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 202-205 °C; Anal. Cald. for $C_{15}H_{16}FN_2O_4P$ +0.25 HBr + 0.5 H_2O: C: 49.02; H: 4.73; N: 7.62. Found: C: 48.90; C: 4.89; N: 7.50.

13.28: 5-Fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{16}FN_2O_4P$ + 0.1 HBr: C: 52.02; H: 4.69; N: 8.09; F: 5.49. Found: C: 52.07; H: 32; N: 7.88; F: 5.61.

13.29: 2-(2-Phosphonofuranyl)-4,5-(2-methylthiazole) benzimidazole. Anal. Cald. for $C_{13}H_{10}N_3O_4PS$ + 2.25 H_2O: C: 41.55; H: 3.89; N: 11.18; S: 8.53. Found: C: 41.69; H: 3.93; N: 10.99; S: 8.81.

13.30: 1-(4-Pyridyl)-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{16}H_{12}N_3PO_4$ + H_20 + 1.25 HBr + 0.5 CH_3CO_2H: C: 41.63; H: 3.55; N: 8.57. Found: C: 41.66; H: 3.52; N: 8.29.

13.31: 2-(2-Phosphonofuranyl)-(4,5-tetramethylene)benzimidazole. Anal. Cald. for $C_{15}H_{15}N_2PO_4$ + 1.5 H_2O: C: 52.18; H: 5.25; N: 8.11. Found: C: 52.09; H: 5.01; N: 7.85.

13.32: 4-Methyl-2-(2-phosphonofuranyl)benzimidazole. Anal. Cald. for $C_{12}H_{11}N_2PO_4$ + H_2O: C: 48.66; H: 4.42; N: 9.46. Found: C: 48.55; H: 4.51; N: 9.16.

13.33: 5-Chloro-1-isopropyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 192 - 195 °C; Anal. Cald. for $C_{14}H_{14}N_2O_4PCl$ + H_2O + 0.1 HBr: C: 45.84; H: 4.42; N: 7.64; Cl=9.67. Found: C: 45.58; H: 4.30; N: 7.47; Cl=10.63.

13.34: 5,6-Difluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{15}F_2N_2O_4P$ + 0.5 H_2O: C: 49.32; H: 4.42; N: 7.67; F: 10.40. Found: C: 49.06; H: 4.20; N: 7.60; F: 10.26.

13.35: 5-Bromo-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_8BrN_2O_4P + H_2O + .05\ HBr$: C: 36.18; H2.77; N: 7.67; Br: 22.98. Found: C: 36.20; H: 2.61; N: 7.45; Br: 22.77.

13.36: 5-Bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{15}H_{16}BrN_2O_4P + .75\ H_2O + .05\ HBr$: C: 43.23; H: 4.24; N: 6.72; Br: 20.13. Found: C: 43.25; H: 4.18; N: 6.59; Br: 20.30.

13.37: 6-Bromo-1-isobutyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{15}H_{16}BrN_2O_4P + H_2O + .05\ HBr$: C: 42.77; H: 4.32; N: 6.65; Br: 19.92. Found: C: 42.49; H: 4.04; N: 6.53; Br: 20.02.

13.38: 4,6-Dichloro-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7N_2O_4PCl_2 + 1.5\ H_2O$: C: 36.69; H: 2.80; N: 7.78; Found: C: 36.91; H: 2.64; N: 7.71.

13.39: 4,6-Dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 155-175 °C; Anal. Cald. for $C_{15}H_{15}N_2O_4PCl_2 + 2/3\ H_2O$: C: 44.90; H: 4.10; N: 6.98. Found: C: 44.96; H: 3.97; N: 6.85.

13.40: 5-Chloro-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{17}H_{12}N_2O_4PCl + 1\ H_2O + 0.1\ HBr$: C: 50.94; H: 3.55; N: 6.99. Found: C: 51.33; H: 3.63; N: 6.54.

13.41: 6-Chloro-1-phenyl-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{17}H_{12}N_2O_4PCl + 0.25\ H_2O + 0.1\ HBr$: C: 52.72; H: 3.28; N: 7.23. Found: C: 52.94; H: 2.99; N: 7.03.

13.42: 4,6-Dibromo-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7Br_2N_2O_4P + 1\ H_2O + 0.1\ HBr$: C: 29.49; H: 2.05; N: 6.25. Found: C: 29.56; H: 2.06; N: 6.16.

13.43: 4,6-Dibromo-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 150-210 °C; Anal. Cald. for $C_{15}H_{15}Br_2N_2O_4P + 0.25\ H_2O + 0.1HBr$: C: 36.72; H: 3.20; N: 5.71. Found: C: 36.72; H: 3.24; N: 5.73.

13.44: 5,6-Dichloro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 225-227 °C; Anal. Cald. for $C_{15}H_{15}Cl_2N_2O_4P + 0.25\ H_2O + 0.1\ HBr$: C: 44.84; H: 3.91; N: 6.97. Found: C: 44.86; H: 3.85; N: 6.81.

13.45: 5,6-Dichloro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 180-210 °C; Anal. Cald. for $C_{15}H_{13}Cl_2N_2O_4P + 0.5\ H_2O + 0.1\ HBr$: C: 44.57; H: 3.52; N: 6.93. Found: C: 44.69; H: 3.45; N: 6.66.

13.46: 5-Chloro-6-fluoro-2-(2-phosphono-5-furanyl)benzimidazole. Anal. Cald. for $C_{11}H_7ClFN_2O_4P + 0.5\ H_2O$: C: 40.58; H: 2.48; N: 8.60. Found: C: 40.58; H: 2.47; N: 8.29.

13.47: 4-Phenyl-6-trifluoromethyl(2-phosphono-5-furanyl) benzimidazole. $C_{18}H_{12}N_2PO_4F_3 + H_2O$: C: 50.72; H: 3.31; N: 6.57. Found: C: 50.58; H: 3.08; N: 6.35.

13.48: 4-Bromo-6-trifluoromethyl(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{12}H_7N_2PO_4F_3Br + H_2O$: C: 33.59; H: 2.11; N: 6.53. Found: C: 33.53; H: 1.86; N: 6.43.

13.49: 5-Chloro-6-fluoro-1-methylcyclopropyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{13}N_2PO_4ClF$: C: 48.60; H: 3.53; N: 7.56. Found: C: 48.32; H: 3.55; N: 7.31.

13.50: 5-Chloro-6-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 196-199; Anal. Cald. for $C_{15}H_{15}ClFN_2O_4P$ + 1.75 H_2O: C: 44.57; H: 4.61; N: 6.93. Found: C: 44.45; H: 4.58; N: 6.87.

13.51: 4-Amino-5-hydroxy-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 206-209 °C; Anal. Cald. for $C_{15}H_{18}N_3O_5P$ + 2.7 H_2O: C: 45.05; H: 5.90; N: 10.51. Found: C: 44.96; H: 5.78; N: 10.14.

13.52: 5-Phosphonomethylenoxy-1,2,3,4-tetrahydropyrido[1,2-a] benzimidazole. mp = 218-222 °C; Anal. Cald. for $C_{12}H_{15}N_2PO_4 + H_2O$ + 0.9 HBr: C: 38.63; H: 4.84; N: 7.51. Found: C: 38.96; H: 4.46; N: 7.41.

13.53: 4,5-Dimethyl-6-bromo-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 205-209 °C; Anal. Cald. for $C_{17}H_{20}PN_2O_4Br$ + 0.25 H_2O: C: 47.29; H: 4.79; N: 6.49. Found: C: 47.25; H: 4.77; N: 6.06.

13.54: 4-Methyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 208-211 °C; Anal. Cald. for $C_{16}H_{19}N_2O_4P + H_2O$ + 0.25 HBr: C: 51.58; H: 5.75; N: 7.52. Found: C: 51.49; H: 5.88; N: 7.41.

13.55: 7-Methyl-1-neopentyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$: C: 58.62; H: 6.08; N: 8.04; Found: C: 58.35; H: 5.97; N: 7.92.

13.56: 6-Chloro-1-neopentyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{16}H_{18}N_2O_4PCl$+0.5 H_2O: C: 50.87 H: 5.07 N: 7.42; C: 50.88 H: 4.82 N: 7.29.

13.57: 5-Chloro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{14}N_2O_4PCl$ + 0.75 H_2O: C: 49.39; H: 4.24; N: 7.68; Found: C: 49.44; H: 4.01; N:7.52.

13.58: 6-Chloro-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{14}N_2O_4PCl$+0. 5 H_2O: C: 49.81; H: 4.18; N: 7.74; Found: C: 49.63; H: 3.93; N: 7.60.

13.59: 5-Phosphonomethylenoxy-1,2,3,4,5,6-hexahydroazapino[1,2-a]benzimidazole. mp=152-156; Anal. Cald. for $C_{13}H_{17}N_2O_4P + H_2O + 0.75$ HBr + 0.5 CH_3CO_2H: C: 41.52; H: 5.41; N: 6.92; Found: C: 41.34; H: 5.58; N: 6.48.

13.60: 1-Isobutyl-4,5-dimethyl-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{20}N_2O_4PCl + 0.5\ H_2O$: C: 52.12 H: 5.40 N: 7.15; Found: C: 52.38; H: 5.23; N: 6.54.

13.61: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-(2-phosphono-5-furanyl)benzimidazole. mp = 219-220°C Anal. Cald. for $C_{17}H_{18}N_2O_4PCl + 1.33\ H_2O$ + 0.1 HBr: C:49.46; H: 4.99; N:6.79; Found: C:49.74; H:4.94 N:6.49.

13.62: 6,7-Dimethyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$: C: 58.62; H: 6.08; N: 8.04; Found: C: 58.78; H: 5.68; N: 7.79.

13.63: 5-Chloro-6,7-dimethyl-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{20}N_2O_4P + 0.25\ H_2O$ + 0.2 HBr: C: 50.61; H:5.17; N: 6.94; Found: C: 50.58; H:4.84; N: 6.58.

13.64: 7-Bromo-5-fluoro-1-isobutyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{15}N_2O_4PBrF + 0.25\ H_2O$; C: 42.73; H: 3.71; N: 6.64; Br: 18.95; Found. C:42.86; H: 3.52; N: 6.49; Br: 19.21.

13.65: 6-Chloro-1-(3-methoxyphenyl)-2-(2-phosphono-5-furanyl) benzimidazole. mp = 184-185° C. Anal. Cald. for $C_{18}H_{14}N_2O_5PCl + 1.75\ H_2O$; C: 49.56; H: 4.04; N: 6.42; Found. C: 49.43; H: 3.71; N: 6.28.

13.66: N-(Phosphonomethyl)benzimidazole-2-carboxamide. mp = 258-260°C. Anal. Cald. for $C_9H_{10}N_3O_4P$ + 0.15 AcOH; C: 42.28; H: 4.04; N: 15.91; Found. C: 42.60; H: 4.02; N: 15.70.

13.67: 1-Isobutyl-5-fluoro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp >250 °C (dec.); Anal. Cald. for $C_{15}H_{15}N_2O_4PBrF + 0.25H_2O$: C: 42.73; H: 3.71; N: 6.64. Found: C: 42.86; H: 3.52; N: 6.49.

13.68: 1-Isobutyl-5-fluoro-6-nitro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 161-165 °C; Anal. Cald. for $C_{15}H_{14}N_3O_6PBrF + 0.25H_2O + 1.0CH_3CO_2H$: C: 38.77; H: 3.54; N: 7.98. Found: C: 39.00; H: 3.49; N: 8.22.

13.69: 1-Isobutyl-5-fluoro-6-amino-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 208-211 °C; Anal. Cald. for $C_{15}H_{16}N_3O_4PBrF + 0.5H_2O + 0.5CH_3CO_2H$: C: 40.78; H: 4.06; N: 8.92. Found: C: 41.18; H: 4.27; N: 8.59.

13.70: 1-Isobutyl-4-amino-5-chloro-6,7-dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_3O_4PCl + 0.2\ H_2O$: C: 49.32; H: 5.16; N: 10.15. Found: C: 49.36; H: 4.94; N: 9.81.

13.71: 1-Isobutyl-5,7-difluoro-6-N,N-dimethylamino-2-(2-phosphono-5-furanyl) benzimidazole. mp = 176-180 °C; Anal. Cald. for $C_{17}H_{20}N_3O_4PF_2$ + 1.0 H_2O + 1.25 Hbr + 0.25 $C_6H_5CH_3$: C: 41.59; H: 4.70; N: 7.76. Found: C: 41.74; H: 4.65; N: 7.39.

13.72: 1-Isobutyl-7-hydroxymethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{16}H_{19}N_2O_5P$ + 0.5H_2O: C: 53.48; H: 5.61; N: 7.80. Found: C: 53.35; H: 5.34; N: 7.48.

13.73: 5-Fluoro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{11}H_7N_2O_4PBrF$ + 0.1 H_2O: C: 36.41; H: 2.00; N: 7.72. Found: C: 36.67; H: 2.28; N: 7.41.

13.74: 4-Nitro-5-fluoro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 218-223 °C (dec.); Anal. Cald. for $C_{11}H_6N_3O_6PF$ + 0.75 H_2O: C: 31.49; H: 1.80; N: 10.01. Found: C: 31.77; H: 2.19; N: 9.41.

13.75: 5-Fluoro-6-nitro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{11}H_6N_3O_6PBrF$ + 0.25 H_2O + 0.25 C_3H_6O: C: 38.77; H: 3.54; N: 7.98. Found: C: 39.00; H: 3.49; N: 8.22.

13.76: 1-Isobutyl-5-fluoro-6-acetamido-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 217-221 °C (dec.); Anal. Cald. for $C_{17}H_{18}N_3O_5PBrF$ + 1.0 H_2O: C: 41.48; H: 4.1; N: 8.54. Found: C: 41.90; H: 4.06; N: 8.08.

13.77: 1-Isobutyl-4-acetamido-5-fluoro-7-ethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{23}N_3O_5PF$ + 1.0 H_2O: C: 51.70; H: 5.71; N: 9.52. Found: C: 52.03; H: 5.56; N: 9.11

13.78: 1-Isobutyl-4-N,N-dimethylamino-5-fluoro-7-ethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{25}N_3O_4PF$ + 1.25 H_2O + 1.5 HBr + 0.33EtOAc: C: 41.91; H: 5.48; N: 7.22. Found: C: 42.09; H: 5.41; N: 6.65.

13.79: 1-Isobutyl-5-fluoro-6-N,N-dimethylamino-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. mp = 183-188 °C; Anal. Cald. for $C_{17}H_{20}N_3O_4PBrF$ + 0.33 H_2O: C: 43.78; H: 4.47; N: 9.01. Found: C: 43.96; H: 4.60; N: 8.56.

13.80: 5-Fluoro-6-chloro-7-ethyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 165-190 °C; Anal. Cald. for $C_{13}H_{11}N_2O_4PClF$ + 1.33 H_2O: C: 42.34; H: 3.74; N: 7.60. Found: C: 42.31; H: 3.64; N: 7.43.

13.81: 1-Isobutyl-4-ethyl-5-chloro-6-Fluoro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PClF$ + 0.33H_2O + 0.25 HBr: C: 47.80; H: 4.70; N: 6.56. Found: C: 47.82; H: 4.66; N: 6.25.

13.82: 4,5,6,7-Tetramethyl-2-(2-phosphono-5-furanyl) benzimidazole. mp = 202-206 °C; Anal. Cald. for $C_{15}H_{17}N_2O4P$ + $1.6H_2O$: C: 51.42; H: 5.85; N: 8.00. Found: C: 51.38; H: 5.75; N: 7.75.

13.83: 1-Isobutyl-4,5,6,7-tetramethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{25}N_2O_4P$ + $0.75H_2O$ + 0.25 HBr: C: 55.64; H: 6.57; N: 6.83. Found: C: 55.67; H: 6.49; N: 6.65.

13.84: 4,6-Dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{13}H_{13}N_2O_4P$ + $1.6H_2O$: C: 48.44; H: 5.11; N: 8.69. Found: C: 48.46; H: 5.08; N: 8.62.

13.85: 1-Isobutyl-4,6-dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$ + 1.0 H_2O. mp = 209-212 °C; C: 55.73; H: 6.33; N: 7.65. Found: C: 55.99; H: 6.21; N: 7.57.

13.86: N-(2-Phosphonomethylacetate)benzimidazole-2-carboxamide. Anal. Cald. for $C_{11}H_{12}N_3O_6P$ + $0.5H_2O$ + 0.25 HBr. mp = 215-218°C; C: 38.58; H: 3.90; N: 12.27; Found. C: 38.94; H: 4.18; N: 12.43.

13.87: 1-Isobutyl-5,7-dimethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{21}N_2O_4P$ + $0.75H_2O$. mp = 196-200 °C; C: 56.43; H: 6.27; N: 7.74. Found: C: 56.47; H: 6.09; N: 7.59.

13.88: 1-Cyclopropylmethyl-4,5,6,7-tetramethyl-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{19}H_{23}N_2O_4P$ + 1.25 H_2O. mp = 207-208 °C; C: 57.50; H: 6.48; N: 7.06. Found: C: 57.32; H: 6.52; N: 7.06.

13.89: 1-Ethyl-4,5-dimethyl-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{16}N_2O_4PCl$ + 1.0 H_2O. C: 48.33; H: 4.87; N: 7.52. Found: C: 48.04; H: 4.81; N: 7.32.

13.90: 1-(4-Bromobutyl)-4,5-dimethyl-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PClBr$. mp = 212-216 °C; C: 44.23; H: 4.15; N: 6.07. Found: C: 44.07; H: 4.26; N: 5.91.

13.91: 4,5-Dimethyl-6-chloro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{13}H_{11}N_2O_4PBrCl$ + 1.33 H_2O. C: 36.35; H:3.21; N: 6.52. Found: C: 36.32; H:3.05; N: 6.41.

13.92: 1-Isobutyl-4,5-dimethyl-6-chloro-7-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PBrCl$. C: 44.23; H:4.15; N: 6.07. Found: C: 44.19; H:4.14; N: 5.88

13.93: 1-Isobutyl-6,7-dimethyl-5-chloro-4-bromo-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{17}H_{19}N_2O_4PBrCl$. mp = 195-201 °C; C: 43.38; H:4.28; N: 5.95. Found: C: 43.67; H:4.32; N: 5.54.

13.94: 1-(4-Aminobutyl)-5-chloro-2-(2-phosphono-5-furanyl) benzimidazole hydrochloric acid salt. Anal. Cald. for $C_{15}H_{18}N_3O4PCl_2$ + $1.5H_2O$ + 1.0 HCl. mp = 236-240 °C (dec.); C: 38.36; H:4.72; N: 8.95. Found: C: 38.13; H:4.64; N: 8.88

13.95: 1-(4-Aminobutyl)-6-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{15}H_{17}N_3O_4PCl$ + 1.0 H_2O. mp = 250-252 °C (dec.); C: 46.46; H:4.94; N: 10.84. Found: C: 46.21; H:4.79; N: 10.62

13.96: 1-Isobutyl-4-methyl-5-chloro-2-(2-phosphono-5-furanyl) benzimidazole. Anal. Cald. for $C_{16}H_{18}N_2O_4PCl$. mp = 193-196 °C; C: 48.19; H:5.39; N: 7.02. Found: C: 48.24; H:5.19; N: 6.85.

<u>Synthesis benzimidazoles with ether linkers :</u>

<u>Example 14.</u>

<u>Preparation of 2-methyl-4-nitrobenzimidazole.</u>

<u>Step 1.</u>

To a solution of 7.0 g (45.7 mmol) 3-nitro-1,2-phenylenediamine in 70 mL of dioxane was added 4.34 mL(46.0 mmol) acetic anhydride and the solution was refluxed overnight. The mixture was cooled to room temperature and the solvents were removed under reduced pressure. The resultant syrup was dissolved in 100 mL of dioxane and 100 mL of 2N sodium hydroxide and was heated to 100° C for 1 h. The reaction was then cooled, concentrated under reduced pressure, and was partitioned between water and ethyl acetate. The organic phase was evaporated to dryness and the solid was washed with water and was dried at 60 °C overnight to yield 7.1 g (40.1 mmol, 87.6 %) of a yellow powder.

<u>Step 2.</u>

<u>Preparation of 1-ethyl-2-methyl-4-nitrobenzimidazole.</u>

To a solution of 0.47 g (2.65 mmol) 2-methyl-4-nitrobenzimidazole, and 0.12 g (2.92 mmol) of sodium hydride in 10 mL of dry dimethylformamide was added 0.218 mL (2.92 mmol) bromoethane. The mixture was heated overnight at 65 °C. The mixture was cooled to room temperature and the solvents were removed under reduced pressure. The resultant syrup was partitioned between water and ethyl acetate. The organic phase was evaporated to dryness and the syrup chromatographed on silica to yield 0.31 g (1.51 mmol, 52%) of a yellow syrup.

Step 3.

Preparation of 1-ethyl-2-bromomethyl-4-nitrobenzimidazole.

To a solution of 0.216 g (1.05 mmol) 1-ethyl-2-methyl-4-nitrobenzimidazole, 50 mL carbon tetrachloride and 0.375 g (2.11 mmol) NBS, was added 50 mg of AIBN. The reaction mixture was heated to 90 °C for five hours and the solution was cooled to room temperature. The solution was concentrated under reduced pressure and the resulting oil was chromatographed on silica to yield 0.16 g (0.57 mmol, 54 %) of a light yellow oil.

Step 4.

Preparation of 1-ethyl-4-nitro-2-[diethyl(methoxymethyl)phosphonate]benzimidazole.

To a solution of 0.191 g (1.14 mmol) diethyl (hydroxymethyl)phosphonate, 0.07 g (1.71 mmol) sodium hydride and 10 mL tetrahydrofuran at 0 °C was added a solution of 0.161 g (0.57 mmol) 1-ethyl-2-bromomethyl-4-nitrobenzimidazole in 10 mL of tetrahydrofuran. The reaction was stirred for 10 minutes at 0 °C and quenched with aqueous saturated ammonium chloride. The reaction contents were concentrated and the resultant solution was partitioned between ethyl acetate and H_2O. The organic layer was separated and dried over sodium sulfate and the solvent was removed under reduced pressure. The resultant oil was chromatographed on silica with 50 % hexane/ethylacetate to yield 0.055 g (0.148 mmol, 26.3 %) of a clear oil.

Step 5.

Preparation of 1-ethyl-4-nitro-2-[3-phospho(methoxymethyl)]benzimidazole.

Followed the procedure given in the Example 12.

Step 6.

Preparation of 1-ethyl-4-amino-2-[3-phospho(methoxymethyl)]benzimidazole.

Followed the procedure given in the Example 9, Method A.

Example 15.

Preparation of 1-isobutyl-4-amino-5-fluoro-7-bromo-2-[3-phospho(methoxymethyl)]benzimidazole.

Step 1.

Synthesis of diethylphosphomethyl acetaldehyde dimethyl acetal ether:

To a solution of 1.0 mmol diethyl (hydroxymethyl)phosphonate, 1.5 mmol of sodium hydride in 2 mL DMF at 0 °C was added a solution of 1.2 mmol of bromoacetaldehyde dimethyl acetal. After 3 h. at room temperature the mixture was diluted with 5 mL of water and extracted with ether (4 x 15 mL). The combined ether layers were concentrated. The residue was chromatographed on a silica gel column eluting with hexane-ethyl acetate (8:1) to yield the product.

Step 2.

Preparation of 1-isobutyl-4-nitro-5-fluoro-7-bromo-2-[3-diethylphospho(methoxymethyl)]benzimidazole:

To a solution of 1.0 mmol of 2-nitro-3-fluoro-5-bromo-6-isobutylamineaniline and 2.0 mmol of diethylphosphomethyl acetaldehyde dimethyl acetal ether in 5 mL THF at 0 °C was added 0.5 mL of 10 % H_2SO_4 and the mixture was heated at 75 °C for 40 min. Solvent was removed under reduced pressure, diluted with water and extracted with EtOAc. The combined EtOAc layers were concentrated. The residue was chromatographed on a silica gel column yield the product.

Step 3.

Followed the procedure given in the Example 4, Method A Step 2.

Step 4.

Preparation of 1-isobutyl-4-amino-5-fluoro-7-bromo-2-[3-diethylphospho(methoxymethyl)]benzimidazole:

Followed the procedure given in the Example 9, Method B.

Step 5.

Followed the procedure given in the Example 12.

15.1: 4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(1-methoxymethyl-3-phosphono)benzimidazole. mp = 200-202 °C(dec.); Anal. Cald. for $C_{13}H_{18}N_3O_4FBrP$: C: 38.07; H: 4.42; N: 10.24. Found: C: 37.87; H: 4.36; N: 10.15.

Example 16.

Benzimidazole phenyl synthesis

Step 1.

Preparation of diethyl-O-formylphenyloxymethylphosphonate.

To a suspension of 1.0 mmol of salicylaldehyde and 1.5 mmol of K_2CO_3 in 3 mL of DMF was added 1.0 mmol of diethyl iodomethylphosphonate and the mixture was heated at 50 °C for 3 days. Extraction and chromatography gave the title compound as an oil.

Step 2.

Preparation of diethyl -2-(4-nitrobenzimidazole-2-yl)phenoxymethyl phosphonate.

A mixture of 1.0 mmol of diethyl-O-formylphenyloxymethyl phosphonate, 1.0 mmol of 3-nitro-1,2-phenylenediamine, and 1.5 mmol of $FeCl_3$ in 5 mL of ethanol was heated at 80 °C for 20 h. Extraction and chromatography gave the title compound. R_f = 0.4 in EtOAc.

Step 3.

Preparation of diethyl 2-(4-nitro-1-ethyl-benzimidazole-2-yl)phenoxymethylphosphonate.

Followed the procedure given in the Example 5, Method A.

Step 4.

Preparation of diethyl 2-(4-amino-1-ethyl-benzimidazole-2-yl)phenoxymethylphosphonate.

Followed the procedure given in the Example 9, Method A.

Step 5.

4-Amino-1-ethyl-2-[1-(2-phosphonomethyloxy)phenyl]benzimidazole.

Followed the procedure given in the Example 12.

Example 17.

Preparation of N-(Phosphonomethyl)benzimidazole-2-carboxamide

Step 1.

To a solution of 1,2-phenylenediamine (5 g, 46.2 mmol) in 100 mL of acetic acid was added trichloromethylacetamidate (8.97 g, 50.8 mmol).The reaction mixture was stirred for 2 h at room temparature. Precipitated solid was filtered and washed with water and dried. The solid was dissolved in 1N KOH solution and stirred for 1 h. The solution was acidified with 3N hydrochloric acid at 0° C until pH 4 and the solid formed was filtered and washed with water. The solid 6.7 g (90%) was dried to give a white powder.(*Eur. J. Med. Chem.*, 1993, *28*: 71)

Step 2.

To a solution of 1.0 g (6.17 mmol) benzimidazole-2-carboxylic acid in 20 mL methylene chloride was added 5 mL diisopropylethylamine and 0.94 g (6.79 mmol) of diethyl(aminomethyl)phosphonate followed by 4.5 g (9.25 mmol) of PyBOP. The reaction contents were stirred at room temperature for 4h, filtered and eluted through a pad of silica with ethyl acetate. The filtrate was evaporated under reduced pressure and was resuspended in a minimum amount of ethyl acetate. The resulting solid was filtered and dried to give 876 mg of a light yellow powder.

Step 3.

Diethylphosphonate hydrolysis was carried out as described in Example 13.

The following compound was prepared in this manner:

17.1: N-(Phosphonomethyl)benzimidazole-2-carboxamide. 250-260 °C (dec.); Anal. cald. for C9H10N3O4P + 0.15 AcOH: C: 42.28; H: 4.04; N: 15.91. Found: C: 42.60; H: 4.02; N: 15.70.

Example 18.

General procedure for the synthesis of acyloxyalkyl phosphonate esters.

Method A:

To a solution of 1 mmol phosphonic acid in 10 mL of DMF or CH_3CN and 3.0 mmol of Hunigs base or *N,N'*-dicyclohexyl-4-morpholinecarboxamidine was added 5.0 mmol of the appropriate alkylating agent (For 6-chloronicotinoyloxymethylchloride, 5-bromonicotinoyloxymethylchloride, benzoyloxymethylchloride, p-fluorophenylchloride,

thiophenecarbonyloxymethylchloride, 2-furoyloxymethylchloride, 3-furoyloxymethylchloride, benzoyloxymethylchloride see ref. US 527033, Oct., 9, 1991 , EP 143 601, June 5, 1985; Chem. Abstr. 104, 5589z, 1986; these chlorides were treated with NaI in CH_3CN to generate the corresponding iodides). The reaction contents were stirred for 2 h and the solvent was removed under reduced pressure. The resultant syrup was chromatographed on silica (ref. EP 0 481 214 A1; J. E. Starrett, et. al. *J. Med. Chem.* **1994** *37*, 1857.).

The following compounds were prepared in this manner:

18.1: 4-Amino-1-isobutyl-2-(5-furanyl-2-bisisobutyryloxymethyl phosphonate)benzimidazole. MF = $C_{23}H_{30}N_3O_8P$; Mass Cald. MH^+ = 508, Obs. MH^+ = 508. R_f = 0.5 in 1:1 EtOAc:Hexane.

18.2: 4-Amino-5,7-dichloro-1-isobutyl-2-(5-furanyl-2-bispivaloyloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{36}N_3O_8PCl_2$: C: 51.27; H: 5.74; N: 6.64; Found: C: 51.22; H: 5.50; N: 6.42.

18.3: 6-Chloro-1-isobutyl-2-(2-bis-pivaloyloxymethylphosphono furan-5-yl) benzimidazole. Anal. Cald. for $C_{27}H_{36}N_2O_8PCl$: C:55.62 H:6.22 N:4.80; C:55.93 H:6.23 N:4.66.

18.4: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bispivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{41}N_3O_8PF$: C: 57.14; H: 6.78; N: 6.89; Found: C: 57.08; H: 6.77; N: 6.70.

18.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis pivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{38}N_2O_8PCl$: C: 57.19; H: 6.29; N: 4.60; Found: C: 56.85; H: 6.31; N: 4.53

18.6: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-thionyl-2-bispivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{38}N_2O_7PSCl$: C: 55.72; H: 6.13; N: 4.48; Found: C: 56.03; H: 6.01; N: 4.46

18.7: 4-Amino-5-fluoro-7-bromo-1-isobutyl-2-(1-methoxymethyl-3-bispivaloyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{36}N_3O_8FBrP$: C: 47.03; H: 6.00; N: 6.58. Found: C: 47.15; H: 6.12; N: 6.31

18.8: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bisisobutyryloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{32}N_2O_8PCl$: C: 54.11; H: 5.81; N: 5.05; Found: C: 54.05; H: 5.72; N: 4.89

18.9: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-thionyl-2-bisbenzoylthiomethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_6PS_2Cl$: C: 58.19; H: 4.44; N: 4.11; Found: C: 58.00; H: 4.50; N: 3.99

18.10: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bisbenzoyloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$ + 0.3Et OAc: C: 59.55; H: 4.72; N: 4.31; Found: C: 59.95; H: 4.36; N: 3.90

18.11: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bisbenzoylthiomethyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_6PS_2Cl$ + 1.25 H_2O: C: 54.95; H: 4.54; N: 4.13; Found: C: 54.92; H: 4.20; N: 3.93

18.12: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-fluoro-benzoyloxymethyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{26}N_2O_8PS_2ClF_2$ + 0.2 CH_2Cl_2: C: 55.44; H: 3.94; N: 4.14; Found: C: 55.43; H: 3.88; N: 3.87

18.13: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(6-chloronicotinoyl) oxymethylphosphonate]benzimidazole. Anal. Cald. for $C_{29}H_{24}N_4O_8PCl_3$: C: 50.20; H: 3.49; N: 8.07; Found: C: 50.43; H: 3.32; N: 7.99

18.14: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(2-furanoyl)oxymethyl phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_{10}PCl$: C: 53.79; H: 4.01; N: 4.65; Found: C: 53.60; H: 4.23; N: 4.68

18.15: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(3-furanoyl)oxymethyl phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_{10}PCl$: C: 53.79; H: 4.01; N: 4.65; Found: C: 53.82; H: 4.08; N: 4.51

18.16: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(2-thiocarbonyl)oxymethyl phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_8PS_2Cl$ + 0.75 H_2O: C: 50.00; H: 3.96; N: 4.32; Found: C: 49.76; H: 3.94; N: 4.34

18.17: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(5-bromonicotinoyl) oxymethylphosphonate]benzimidazole. Anal. Cald. for $C_{29}H_{24}N_4O_8PClBr_2$ + 0.1 EtOAc + 1.6 H_2O:C: 43.04; H: 3.44; N: 6.83; Found: 43.28; H: 3.36; N: 6.46

<u>Method B:</u>

A suspension of 1 mmol of phosphonic acid in 5 mL of thionyl chloride was heated at reflux temperature for 4 h. The reaction mixture was cooled and evaporated to dryness. To the resulting residue was added a solution of 4 mmol of benzoylthioethanol (ref. Lefebvre, I. et al. *J. Med. Chem.* 38, 3941, 1995; Benzaria, S. et al. *J. Med. Chem.* 39, 4958, 1996) and 2.5 mmol pyridine in 3 mL of methylene chloride. After stirring at 25 °C for 4 h the reaction was subjected to work up and chromatography.

The following compounds were prepared in this manner:

18.18: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis(benzoylthioethylphosphonate) benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_6PS_2Cl$: C: 58.02; H: 4.72; N: 4.10; Found: C: 57.90; H: 4.72; N: 4.04

18.19: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-[5-furanyl-2-bis(benzoyloxy-3-butyl)phosphonate]benzimidazole. Anal. Cald. for $C_{39}H_{45}N_3O_8PF$ + 0.5 H_2O: C: 63.06; H: 6.24; N: 5.66; Found: C: 62.86; H: 6.13; N: 5.46

18.20: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis (benzoyloxy-3-butyl)phosphonate]benzimidazole. Anal. Cald. for $C_{39}H_{42}N_2O_8PCl$ + 1.0 H_2O: C: 62.36; H: 5.90; N: 3.73; Found: C: 62.32; H: 5.80; N: 3.65

18.21: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis(acetyloxyethylphosphonate) benzimidazole. Anal. Cald. for $C_{23}H_{28}N_2O_8PCl$ + 0.2 H_2O: C: 52.07; H: 5.40; N: 5.28; Found: C: 51.67; H: 5.40; N: 5.07

18.22: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl)-2-bisacetylthioethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{33}N_3O_6PFS_2$ + 0.2 CH_2Cl_2 + 0.1 $PhCH_3$; C: 50.84; H: 5.63; N: 6.87 Found: C:50.74; H: 5.54 N: 6.48.

Example 19.

General procedure for hydroxyethyldisulfidylethylphosphonate diester.

A suspension of 1 mmol of phosphonic acid in 5 mL of thionyl chloride was heated at reflux temperature for 4 h. The reaction mixture was cooled and evaporated to dryness. To the resulting residue was added a solution of 4 mmol of 2-hydroxyethyl disulfide and 2.5 mmol pyridine in 3 mL of methylene chloride. After stirring at 25 °C for 4 h the reaction was subjected to work up and chromatography.

The following compounds were prepared in this manner:

19.1: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bis(hydroxyethyldisulfidylethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{37}N_3O_6PFS_4$ + 0.7 H_2O; C: 45.06; H: 5.81; N: 6.31; Found: C: 45.24; H: 5.67; N: 5.93.

19.2: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis(hydroxyethyldisulfidylethylphosphonate)benzimidazole. Anal. Cald. for

$C_{23}H_{32}N_2O_6PClS_4$ + 0.5 H_2O: C: 43.42; H: 5.23; N: 4.40; Found: C: 43.12; H: 4.94; N: 4.26.

Example 20.

General procedure for substituted-benzyl phosphonate diesters.

Followed the same procedure as in Example 18, Method B.

The following compounds were prepared in this manner:

20.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p*-chlorobenzylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_4PCl_3$ + 0.25 H_2O: C: 58.69; H: 4.53; N: 4.42; Found: C: 58.48; H: 4.62; N: 4.19

20.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p*-acetoxybenzylphosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{34}N_2O_8PCl$: C: 62.09; H: 5.06; N: 4.14; Found: C: 61.69; H: 4.93; N: 4.10

20.3: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-dimethoxybenzylphosphonate)benzimidazole. Anal. Cald. for $C_{37}H_{40}N_2O_{12}PCl$ + $0.4C_6H_5CH_3$: C: 59.16; H: 5.39; N: 3.47; Found: C: 59.19; H: 5.16; N: 3.34

20.4: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-methylbenzyl phosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{36}N_2O_8PCl$ + 2.0 H_2O + $0.5C_6H_5CH_3$: C: 60.75; H: 5.83; N: 3.68; Found: C: 60.82; H: 5.55; N: 3.32

20.5: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-methoxybenzyl phosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{36}N_2O_{10}PCl$ + 1.2 H_2O: C: 57.37; H: 5.28; N: 3.82; Found: C: 57.44; H: 5.16; N: 3.60

20.6: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxy-*m*-chlorobenzyl phosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_8PCl_3$: C: 55.06; H: 4.20; N: 3.89; Found: C: 54.76; H: 4.33; N: 3.64

20.7: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-benzylphosphonate) benzimidazole. Anal. Cald. for $C_{29}H_{28}N_2O_4PCl$: C: 62.99; H: 5.47; N: 5.07; Found: C: 62.76; H: 5.84; N: 5.20

20.8: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*p,m*-diacetoxybenzylphosphonate)benzimidazole. Anal. Cald. for $C_{37}H_{36}N_2O_{12}PCl$ + 0.5 H_2O: C: 57.26; H: 4.81; N: 3.61; Found: C: 57.02; H: 4.84; N: 3.52.

Example 21.

General procedure for phenyl phosphonate diesters.

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

21.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-(5,6,7,8-tertahydro-2-napthyl)phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{38}N_2O_4PCl$: C: 69.31; H: 5.97; N: 4.37; Found: C: 69.33; H: 6.07; N: 4.14

21.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-phenyl phosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{26}N_2O_4PCl$: C: 64.63; H: 4.99; N: 5.20; Found: C: 64.58; H: 4.99; N: 5.21

21.3: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*o*-ethoxyphenylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{34}N_2O_6PCl$ + 0.67 H_2O: C: 62.60; H: 5.63; N: 4.42; Found: C: 62.57; H: 5.80; N: 4.24

21.4: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-mono-*o*-ethoxyphenylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{26}N_2O_5PCl$ + 1.5 H_2O + 0.1HCl: C: 56.49; H: 5.52; N: 5.27; Found: C: 56.22; H: 5.24; N: 5.01

21.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bis-*o*-methoxyphenylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{30}N_2O_6PCl$: C: 62.79; H: 5.10; N: 4.72; Found: C: 62.79; H: 5.30; N: 4.54

21.6: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-phenyl phosphonate) benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_4PCl$ + $0.5H_2O$: C: 62.86; H: 4.88; N: 5.43; Found: C: 62.72; H: 4.75; N: 5.54

21.7: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*o*-acetoxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$: C: 59.77; H: 4.53; N: 4.50; Found: C: 59.33; H: 4.82; N: 4.21

21.8: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetoxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$: C: 59.77; H: 4.53; N: 4.50; Found: C: 59.46; H: 4.67; N: 4.34

21.9: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-*p*-(4-morpholino)phenyl phosphonate]benzimidazole. Anal. Cald. for $C_{35}H_{38}N_4O_6PCl$ + 0.5 H_2O: C: 61.27; H: 5.73; N: 8.17; Found: C: 61.62; H: 5.78; N: 7.79

21.10: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-hydroxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{27}H_{24}N_2O_6PCl$ + 0.75 H_2O: C: 58.70; H: 4.65; N: 5.07; Found: C: 58.54; H: 4.43; N: 4.78

21.11: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*m*-acetoxyphenylphosphonate) benzimidazole. Anal. Cald. for $C_{31}H_{28}N_2O_8PCl$ + 0.4 H_2O: C: 59.08; H: 4.61; N: 4.45; Found: C: 58.82; H: 4.54; N: 4.20

21.12: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(1-triozolo)acetoxyphenyl phosphonate]benzimidazole. Mass. Cald. for $C_{31}H_{26}N_8O_4PCl$: 641(M + H); Found: 641(M + H)

21.13: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-*m*-(*N,N*-dimethylamino) phenylphosphonate]benzimidazole. Anal. Cald. for $C_{31}H_{34}N_4O_4PCl$ + 1.5 H_2O + 0.35 CH_2Cl_2: C: 57.95; H: 5.85; N: 8.62; Found: C: 57.94; H: 5.49; N: 8.24

21.14: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-acetamidophenyl phosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{30}N_4O_6PCl$ + 0.5 H_2O: C: 59.10; H: 4.96; N: 8.89; Found: C: 59.03; H: 5.23; N: 9.68

21.15: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bis(2-methylphenylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{33}N_3O_4PF$ + 0.7 H_2O; C: 64.84; H: 6.04; N: 7.32; Found: C: 64.88; H: 6.12; N: 7.10.

21.16: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bis(phenylphosphonate)benzimidazole. Anal. Cald. for $C_{29}H_{29}N_3O_4PF$ + 0.3 H_2O; C: 64.63; H: 5.54; N: 7.80; Found: C: 64.61; H: 5.57; N: 7.47.

Example 22.

Preparation of (5-substituted 2-oxo-1,3-dioxolen-4-yl)methyl phosphonate prodrugs.

A solution of 1 mmol phosphonic acid in DMF and 2 mmol of sodium hydride was treated with 4 mmol of 5-substituted-4-bromomethyl-2-oxo-1,3-dioxolene (prepared according to *Chem. Pharm. Bull.* **1984**, *32(6)*, 2241.) at 25 °C for 24 h. Extraction and chromatography gave the phosphonate prodrug. The following compound was prepared in this manner:

22.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methylphosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{26}N_2O_{10}PCl$ + 0.75 H_2O: C: 62.79; H: 5.10; N: 4.72; Found: C: 62.79; H: 5.30; N: 4.54

Example 23.

General procedure for the synthesis of alkyloxycarbonyloxyalkyl phosphonate esters.

To a solution of 1 mmol phosphonic acid in 5 mL of anhydrous DMF was added 5 mmol of *N,N'*-dicyclohexyl-4-morpholinecarboxamidine followed by 5 mmol of isopropyloxycarbonyloxymethyliodide (all the alkyl and aryloxy(thio)carbonyloxymethyl iodides were prepared from the commercially available chloromethyl chloroformate according to the reported procedure, Tatsuo Nishimura et al. *J. Antibiotics*, **1987**, 40(1), 81-90). The reaction contents were stirred for 24 h at room temperature and the solvent was removed

under reduced pressure. The resultant syrup was chromatographed on silica with 50% EtOAc/Hexanes to yield the required product.

The following compounds were prepared in this manner:

23.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-biscyclohexyloxycarbonyloxymethylphosphonate)benzimidazole. mp = 120-122 °C; Anal. Cald. for $C_{33}H_{42}N_2O_{10}PCl$: C: 57.18; H: 6.11; N: 4.04; Found: C: 57.16; H: 6.13; N: 3.99

23.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisethyloxycarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{32}N_2O_{10}PCl$: C: 51.16; H: 5.50; N: 4.77; Found: C: 51.06; H: 5.30; N: 4.72

23.3: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisisopropyloxycarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{34}N_2O_{10}PCl$: C: 52.90; H: 5.59; N: 4.57; Found: C: 52.96; H: 5.56; N: 4.49

23.4: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisisopropylthiocarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{27}H_{34}N_2O_8PClS_2$: C: 50.27; H: 5.31; N: 4.34; Found: C: 49.99; H: 5.35; N: 4.27

23.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisphenylthiocarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_8PClS_2$: C: 55.58; H: 4.24; N: 3.93; Found: C: 55.36; H: 4.43; N: 3.77

23.6: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisphenyloxy carbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{30}N_2O_{10}PCl$ + 0.5 H_2O: C: 55.58; H: 4.24; N: 3.93; Found: C: 55.36; H: 4.43; N: 3.77

23.7: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bismethyloxy carbonyloxymethylphosphonate)benzimidazole. mp = 87-85 °C; Anal. Cald. for $C_{33}H_{30}N_2O_8PClS_2$: C: 55.58; H: 4.24; N: 3.93; Found: C: 55.36; H: 4.43; N: 3.77

23.8: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-(5-furanyl-2-bisethyloxy carbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{25}H_{33}N_3O_{10}FP$: C: 51.28; H: 5.68; N: 7.18. Found: 51.51; H: 5.83; N: 7.18

23.9: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-methoxyphenyloxy carbonyl oxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{12}PCl$: C: 55.43; H: 4.51; N: 3.92; Found: C: 55.52; H: 4.56; N: 3.47

23.10: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*o*-methoxyphenyloxycarbonyloxy methylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{12}PCl$: C: 55.43; H: 4.51; N: 3.92; Found: C: 55.34; H: 4.62; N: 3.66

23.11: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*m*-methoxyphenyloxycarbonyloxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{12}PCl$: C: 55.43; H: 4.51; N: 3.92; Found: C: 55.28; H: 4.68; N: 3.83

23.12: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*o*-methylphenyloxycarbonyl oxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{33}H_{32}N_2O_{10}PCl$: C: 58.03; H: 4.72; N: 4.10; Found: C: 57.78; H: 4.60; N: 3.89

23.13: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-*p*-chlorophenyloxycarbonyl oxymethylphosphonate)benzimidazole. Anal. Cald. for $C_{31}H_{26}N_2O_{10}PCl_3$: C: 51.44; H: 3.62; N: 3.87; Found: C: 51.46; H: 3.86; N: 3.81

23.14: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-1,4-biphenyloxycarbonyl oxymethylphosphonate)benzimidazole. mp = 112-114 °C; Anal. Cald. for $C_{43}H_{36}N_2O_{10}PCl$: C: 63.98; H: 4.50; N: 3.47; Found: C: 63.90; H: 4.39; N: 3.38

23.15: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bis-phthalylethyloxycarbonyloxy methylphosphonate)benzimidazole. mp = 112-114 °C; Anal. Cald. for $C_{43}H_{36}N_2O_{10}PCl$: C: 63.98; H: 4.50; N: 3.47; Found: C: 63.90; H: 4.39; N: 3.38

23.16: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(*N*-Phenyl, *N*-methylcarbamoyl) oxymethylphosphonate]benzimidazole. Anal. Cald. for $C_{33}H_{34}N_4O_8PCl$ + 0.25 HI + 0.66 H_2O: C: 54.67; H: 4.95; N: 7.73; Found: 54.71; H: 4.76; N: 7.44

23.17: 6-Chloro-1-isobutyl-2-[5-furanyl-2-mono-(4-morpholinocarbonyloxy methyl)phosphonate]benzimidazole. Anal. Cald. for $C_{21}H_{25}N_3O_7PCl$ + 0.5 HI + 0.25 H_2O: C: 44.54; H: 4.63; N: 7.42; Found: 44.59; H: 4.52; N: 7.56

Example 24.

General procedure for the substituted-ethyl phosphonate diesters.

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

24.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-(2-trichloroethyl)phosphonate]benzimidazole. mp = 132-134 °C; Anal. Cald. for $C_{21}H_{20}N_2O_4PCl_7$: C: 39.19; H: 3.13; N: 4.35; Found: C: 39.37; H: 3.28; N: 4.18

24.2: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-(2-bromoethyl)phosphonate]benzimidazole. Anal. Cald. for $C_{21}H_{24}N_2O_4PClBr_2$: C: 42.42; H: 4.07; N: 4.71; Found: C: 42.64; H: 4.35; N: 4.65

24.3: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(2-azidoethyl)phosphonate] benzimidazole. mp = 73-75 °C; Anal. Cald. for $C_{19}H_{22}N_8O_4PCl$: C: 46.30; H: 4.50; N: 22.74; Found: C: 46.30; H: 4.39; N: 22.51

The azido compound (**24.3**) was obtained by reaction of the compound 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(2-iodoethyl)phosphonate]benzimidazole and sodium azide in DMF.

24.4: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-(2-aminoethyl)phosphonate] benzimidazole hydrogen chloride salt. mp = 160 °C; Anal. Cald. for $C_{19}H_{26}N_4O_4PCl.3HCl + 1.0\ H_2O$: C: 40.16; H: 5.50; N: 9.80; Found: C: 39.88; H: 5.41; N: 9.43

The amino compound (**24.4**) was obtained by the hydrogenation of the azido compound (**24.3**) in presence of 10 % Pd/C and HCl in EtOAc.

24.5: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis(2-iodoethyl)phosphonate]benzimidazole. Anal. Cald. for $C_{21}H_{24}N_2O_4PClI_2$: C: 34.44; H: 3.35; N: 4.23; Found: C: 34.69; H: 3.12; N: 4.01.

24.6: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(2-*N,N*-dimethylaminoethyl)phosphonate]benzimidazole hydrogen chloride salt. mp = 61-63° C; Anal. Cald. for $C_{23}H_{34}N_4O_4PCl$: C: 55.59; H: 6.90; N: 11.27; Found: C: 55.34; H: 7.06; N: 11.07.

Example 25.

General procedure for the synthesis of phosphonoamidates. (ref. Starret, J. E. et al. *J. Med. Chem.* 37, 1857, **1994**).

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

25.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-cyclic (2,2-dimethylpropyl)phosphonoamidate]benzimidazole. mp = 132-134 °C; Anal. Cald. for $C_{21}H_{20}N_2O_4PCl_7$: C: 39.19; H: 3.13; N: 4.35; Found: C: 39.37; H: 3.28; N: 4.18

Example 26.

General procedure for the synthesis of substituted amidoalkyl esters. (ref. Starret, J. E. et al. *J. Med. Chem.* 37, 1857, **1994**).

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

26.1: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis-{*N,N*(2-hydroxyethyl)amido methyl} phosphonate]benzimidazole. Anal. Cald. for $C_{27}H_{38}N_4O_{10}PCl$ + 0.4 CH_2Cl_2 + 1.0 MeOH: C: 47.97; H: 6.07; N: 7.88; Found: C: 47.69; H: 5.88; N: 7.53

Example 27.

General procedure for the synthesis of alkyloxycarbonylalkyl esters. (ref. Serafinowska, H. T., et. al. *J. Med. Chem.* **1995** *38*, 1372).

Followed the same procedure as in Example 18, Method A

The following compounds were prepared in this manner:

27.1: 6-Chloro-1-isobutyl-2-(5-furanyl-2-bismethyloxycarbonylmethyl phosphonate)benzimidazole. Anal. Cald. for $C_{21}H_{24}N_2O_8PCl$ + 1.0 H_2O: C: 50.56; H: 4.85; N: 5.62; Found: C: 50.53; H: 5.02; N: 5.56

Example 28.

General procedure for the synthesis of substituted-phenylalkyl esters.

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

28.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-(5-furanyl-2-bisphenpropylphosphonate)benzimidazole. Anal. Cald. for $C_{35}H_{38}N_2O_4PCl$: C: 68.12; H: 6.21; N: 4.54; Found: C: 67.87; H: 6.32; N: 4.49

28.2: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p*-acetoxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{40}N_2O_8PCl$ + 0.2 H_2O: C: 62.53; H: 5.73; N: 3.94; Found: C: 62.14; H: 5.67; N: 3.88

28.3: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(3-phenyl-3-acetoxypropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{34}H_{40}N_2O_8PCl$ + 1.85 H_2O: C: 62.02; H: 5.95; N: 3.78; Found: C: 59.63; H: 6.14; N: 3.55

28.4: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p*-hydroxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{33}H_{36}N_2O_6PCl$ + 0.08 H_2O: C: 63.48; H: 5.84; N: 4.49; Found: C: 63.05; H: 5.69; N: 4.32

28.5: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p*-methoxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{35}H_{40}N_2O_6PCl$: C: 64.56; H: 6.19; N: 4.30; Found: C: 64.20; H: 6.13; N: 4.08

28.6: 6-Chloro-1-isobutyl-2-[5-furanyl-2-bis(*p,m*-dimethoxyphenpropyl) phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{44}N_2O_0PCl$: C: 62.49; H: 6.24; N: 3.94; Found: C: 62.06; H: 6.02; N: 3.62

Example 29.

General procedure for the synthesis of substituted phthalimide esters.

To a solution of 1 mmol phosphonic acid in 10 mL of DMF or CH_3CN and 3.0 mmol of Hunigs base or *N,N'*-dicyclohexyl-4-morpholine carboxamidine is added 5.0 mmol of the substituted 3-bromophthalide. The reaction contents are stirred for 2 h and the solvent is removed under reduced pressure. The resultant syrup is chromatographed on silica(Clayton, J. P. et al. *J. Med. Chem.* **1976** *19*, 1385.).

Example 30:

General procedure for cyclic 1,3-cyclohexyl phosphonate diesters:

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

30.1: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-[1-hydroxy-3,5-cyclohexylphosphono-5-furanyl]benzimidazole. mp = 211 - 215°C; Anal. Cald. for $C_{23}H_{26}ClN_2O_5P$ + 2/3 H_2O: C: 56.50; H: 5.64; N: 5.73. Found: C: 56.65; H: 5.54 ; N: 5.64.

30.2: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-[1-acetylhydroxy-3,5-cyclohexylphosphono-5-furanyl]benzimidazole, minor isomer; Anal. Cald. for $C_{25}H_{28}ClN_2O_6P$ + 1.5 H_2O: C: 55.00 ; H: 5.72; N: 5.13. Found: C: 55.19; H: 5.31; N: 4.65.

30.3: 6-Chloro-4,5-dimethyl-1-cyclopropylmethyl-2-[1-acetylhydroxy-3,5-cyclohexylphosphono-5-furanyl]benzimidazole, major isomer; Anal. Cald. for $C_{25}H_{28}ClN_2O_6P$ + 0.75 H_20 + 0.1 EtOAc: C: 56.37; H: 5.64; N: 5.18. Found: C: 56.68; H: 5.69; N: 4.80.

30.4: 6-Chloro-1-isobutyl-2-{2-[5-(1-hydroxy-3,5-cyclohexyl)phosphono] furanyl}benzimidazole, minor isomer. mp >220°C; Anal. Cald. for $C_{21}H_{24}ClN_2O_5P$ + 1/3 H_2O: C: 55.21; H: 5.44; N: 6.13. Found: C: 55.04; H: 5.50; N: 6.00.

30.5: 6-Chloro-1-isobutyl-2-{2-[5-(1-hydroxy-3,5-cyclohexyl)phosphono] furanyl}benzimidazole, major isomer. mp >220°C; Anal. Cald. for $C_{21}H_{24}ClN_2O_5P$: C: 55.94; H: 5.37; N: 6.21. Found: C: 55.73; H: 5.34; N: 6.13.

Example 31:

General procedure for the cyclic substituted 1,3-propyl phosphonate diesters:

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

31.1: 6-Chloro-1-isobutyl-2-(2-(5-(1-R-phenyl-1,3-propyl)phosphono)furanyl) benzimidazole, major isomer. mp = 204 - 206 °C; Anal. Cald. for $C_{24}H_{24}ClN_2O_4P$: C: 61.22; H: 5.14; N: 5.95. Found: C: 60.95; H: 5.01; N: 5.88.

31.2: 6-Chloro-1-isobutyl-2-(2-(5-(1-R-phenyl-1,3-propyl)phosphono) furanyl)benzimidazole, minor isomer; Anal. Cald. for $C_{24}H_{24}ClN_2O_4P + H_2O$: C: 58.96; H: 5.36; N: 5.73. Found: C: 58.85; H: 5.48; N: 5.55.

The two diastereomers were separated by column chromatography by eluting with methanol-methylene chloride (5:95).

31.3: 6-Chloro-1-isobutyl-2-{5-[1S-(4-nitrophenyl)-2R-acetylamino-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, major isomer; MH^+ Cald. for $C_{26}H_{26}ClN_4O_7P$: 573.Found: 573.

31.4: 6-Chloro-1-isobutyl-2-{5-[1S-(4-nitrophenyl)-2R-acetylamino-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, minor isomer; Anal. Cald. for $C_{26}H_{26}ClN_4O_7P + 1.6\ H_2O + 0.25\ CH_2Cl_2$: C:50.61; H: 4.81; N: 8.99. Found: C: 50.25; H: 4.37; N: 9.01.

31.5: 6-Chloro-1-isobutyl-2-{5-[1S-(4-methylthiophenyl)-2S-acetylamino-propan-1,3-yl]phosphono-2-furanyl}benzimidazole; Anal. Cald. for $C_{27}H_{29}ClN_3O_5PS + 1\ H_2O + 0.35\ CH_2Cl_2$: C: 52.83; H: 5.14; N: 6.76. Found: C: 52.44; H: 4.76; N: 6.59 .

All three diastereomers were separated by column chromatography by eluting with methanol-methylene chloride (5:95). The substituted 1,3-diol to prepare **31.3, 31.4, 315** was made by the following method.

To a solution of D-threo-2-amino-1-(4-nitrophenyl)-1,3-propane diol (2.0 g, 9.4 mmol) in pyridine (20 mL) was added acetic anhydride (0.9 mL, 9.4 mmol) slowly at 0°C. The reaction was warmed to room temperature and allowed to stir for 1h. Reaction mixture was concentrated under reduced pressure and

azeotroped. Column chromatography by elution with ethyl acetate-methylene chloride (4:1) resulted in 1.7 g of pure acetylated product.

31.6: 6-Chloro-1-isobutyl-2-{5-[1-(2-pyridyl)-propan-1,3-yl] phosphono-2-furanyl}benzimidazole. Anal. Cald. for $C_{23}H_{23}ClN_3O_4P$ + 1.5 H_2O + 0.3 CH_2Cl_2: C: 53.37; H: 5.11; N: 8.01. Found: C: 53.23; H: 4.73 ; N: 7.69.

31.7: 6-Chloro-1-isobutyl-2-{5-[1-(N-oxo-2-pyridyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 195.0 °C (dec.); Anal. Cald. for $C_{23}H_{23}ClN_3O_5P$ + 0.25 H_2O + 0.25 CH_2Cl_2: C: 54.37; H: 4.71; N: 8.18. Found: C: 54.77; H: 4.86; N: 7.76.

31.8: 6-Chloro-1-isobutyl-2-{5-[1-(4-pyridyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 165.0 °C (dec.); Mass Cald. for $C_{23}H_{23}ClN_3O_4P$: MH^+ 454 : Found: MH^+ 454

The substituted 1,3-diol used to prepare **31.6, 31.8** were made by the following 2 step method.

Step A: (*J. Org. Chem.*, **1957**, 22, 589)

To a solution of 2-pyridinepropanol (10 g, 72.9 mmol) in acetic acid (75 mL) was added 30% hydrogen peroxide slowly. The reaction mixture was heated to 80 °C for 16 h. The reaction was concentrated under vacuum and the residue was dissolved in acetic anhydride (100 mL) and heated at 110 °C overnight. Acetic anhydride was evaporated upon completion of reaction. Chromatography of the mixture by eluting with methanol-methylene chloride (1:9) resulted in 10.5 g of pure diacetate.

Step B:

To a solution of diacetate (5 g, 21.1 mmol) in methanol-water (3:1, 40 mL) was added potassium carbonate (14.6 g, 105.5 mmol). After stirring for 3 h at room temperature, the reaction mixture was concentrated. The residue was chromatographed by eluting with methanol-methylene chloride (1:9) to give crystalline diol.

The compound **31.7** was prepared by the oxidation of the compound **31.6** by the following method.

To a solution of 6-chloro-1-isobutyl-2-{5-[1-(2-pyridyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole (172 mg, 0.36 mmol) in methylene chloride was added 3-chloroperoxybenzoic acid (252 mg, 0.72 mmol) at 0°C. The reaction was warmed to room temperature and allowed stir for 3h. The

solvent was evaporated under reduced pressure. Chromatography by elution with methanol-methylenecchloride (5:95) resulted in 100 mg of pure N-oxide.
31.9: 6-Chloro-1-isobutyl-2-{5-[1-(4-fluorophenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 207 - 208 °C; Anal. Cald. for $C_{24}H_{23}ClFN_2O_4P$: C: 58.96; H: 4.74; N: 5.73. Found: C: 59.20; H: 4.64; N: 5.59.
31.10: 6-Chloro-1-isobutyl-2-{5-[1-(4-fluorophenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 176 - 179°C; Anal. Cald. for $C_{24}H_{23}ClFN_2O_4P$ + $0.5H_2O$: C: 57.90; H: 4.86; N: 5.63. Found: C: 57.60; H: 4.68; N: 5.54.

The substituted 1,3-diol used to prepare **31.9, 31.10** was made by the following 3 step method.

<u>StepA:</u> (*J. Org. Chem.*, **1988**, 53, 911)

To a solution of oxalyl chloride (5.7 mL, 97 mmol) in dichloromethane (200 mL) at -78°C was added dimethyl sulfoxide (9.2 mL, 130 mmol). The reaction mixture was stirred at -78° C for 20 min. before addition of 3-(benzyloxy)propan-1-ol (11 g, 65 mmol) in dichloromethane (25 mL). After an hour at -78°C, reaction was quenched with triethylamine (19 mL, 260 mmol) and warmed to room temperature. Work-up and column chromatography by elution with dichloromethane resulted in 8 g of 3-(benzyloxy)propan-1-al.

<u>Step B:</u>

To a solution of 3-(benzyloxy)propan-1-al (1 g, 6.1 mmol) in THF at 0° C was added a 1M solution of 4-fluorophenylmagnesium bromide in THF (6.7 mL, 6.7 mmol). The reaction was warmed to room temperature and stirred for 1 h. Work-up and column chromatography by elution with dichloromethane resulted in 0.7 g of alcohol.

<u>Step C:</u>

To a solution of benzyl ether (500 mg) in ethyl acetate (10 mL) was added 10%$Pd(OH)_2$-C (100 mg). The reaction was stirred under a hydrogen atmosphere for 16 h. The reaction mixture was filtered through Celite and concentrated. Chromatography of the residue by elution with ethyl acetate-dichloromethane (1:1) resulted in 340 mg of product.

31.11: 6-Chloro-1-isobutyl-2-{5-[1-(3-bromo-4-methoxyphenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, major isomer. mp = 167 - 169 °C; Anal. Cald. for $C_{25}H_{25}BrClN_2O_5P$: C: 51.79; H: 4.35; N: 4.83. Found: C: 51.77; H: 4.25; N: 4.73.

31.12: 6-Chloro-1-isobutyl-2-{5-[1-(3-Bromo-4-methoxyphenyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole, minor isomer. Anal. Cald. for $C_{25}H_{25}BrClN_2O_5P$ + $0.55CHCl_3$: C: 47.54; H: 3.99; N: 4.34. Found: C: 47.50; H: 3.89; N: 3.99.

The substituted 1,3-diol to prepare **31.11, 31.12** was made by the following 2 step method.

Step A: (*J. Org. Chem.*, **1990**, 55, 4744)

To a solution of diisopropylamine (4.1 mL, 29.4 mmol) in ether (40 mL) at -78 °C was added 2.5M n-butyl lithium (11.8 mL, 29.4 mmol). The reaction was stirred for 15 min before adding t-butyl acetate (4 mL, 29.4 mmol) in ether (10 mL). After 20 min, aldehyde (3g, 14 mmol) in ether (10 mL) was added and warmed to room temperature where it was stirred for 16 h. Work-up and column chromatography by elution with ethyl acetate-dichloromethane (1:9) resulted in 3.3 g of addition product.

Step B:

To a solution of t-butyl ester (1.5 g, 4.5 mmol) in THF (20 mL) was added 1M lithium aluminum hydride at 0° C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with ethyl acetate and saturated aq. sodium sulfate was added to precipitate the salts. Filtration and concentration of solvent resulted in crude diol. Column chromatography by elution with ethyl acetate-dichloromethane (1:1) gave 970 mg of pure diol.

31.13: 6-Chloro-1-isobutyl-2-{5-[2-(hydroxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 164 - 165 °C; Anal. Cald. for $C_{19}H_{22}ClN_2O_5P$: C: 53.72; H: 5.22; N: 6.59. Found: C: 53.62; H: 5.18; N: 6.42.

31.14: 6-Chloro-1-isobutyl-2-{5-[2-(acetoxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 132 - 134 °C; Anal. Cald. for $C_{21}H_{24}ClN_2O_6P$: C: 54.03; H: 5.18; N: 6.00 . Found: C: 54.17; H: 4.99 ; N: 5.81.

31.15: 6-Chloro-1-isobutyl-2-{5-[2-(methoxycarbonyloxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 138 - 140 °C; Anal. Cald. for $C_{21}H_{24}ClN_2O_7P$: C: 52.24; H: 5.01; N: 5.80. Found: C: 52.13; H: 5.07; N: 5.51.

31.16: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-{5-[2-(acetoxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole; Anal. Cald. for $C_{23}H_{29}FN_3O_6P$ + 0.3 H_2O: C: 55.38; H: 5.98; N: 8.42. Found: C: 55.60; H: 6.31; N: 8.02.

31.17: 6-Amino-9-neopentyl-8-{5-[2-(acetoxymethyl)-propan-1,3 -yl]phosphono-2-furanyl}purine. mp = 164 - 165 °C; Anal. Cald. for

$C_{20}H_{26}N_5O_6P$: C: 51.84; H: 5.65; N: 15.11 . Found: C: 52.12; H: 5.77 ; N: 14.59.

31.18: 4-Amino-5-fluoro-7-ethyl-1-isobutyl-2-{5-[2-(cyclohexylcarbonyloxymethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 60-63° C; Anal. Cald. for $C_{28}H_{37}FN_3O_6P$: C: 59.89; H: 6.64; N: 7.48. Found: C: 59.97; H: 6.60; N: 7.33.

31.19: 6-Chloro-1-isobutyl-2-{5-[2-(aminomethyl)-propan-1,3-yl]phosphono-2-furanyl}benzimidazole. mp = 158 - 160° C; Anal. Cald. for $C_{19}H_{23}ClN_3O_4P$: C: 51.13; H: 5.76; N: 9.41. Found: C: 51.35; H: 5.48; N: 9.05.

The substituted 1,3-diol to prepare **31.16** was made by the following method.

Monoacetylation of 2-(hydroxymethyl)-1,3-propanediol:

To a solution of 2-(hydroxymethyl)-1,3-propanediol (1 g, 9.4 mmol) in pyridine (7.5 mL) at 0° C was added acetic anhydride (0.89 mL, 9.4 mmol) slowly. The resulting solution was warmed to room temperature and stirred for 16 h. The reaction was concentrated under reduced pressure and chromatographed by eluting with methanol-dichloromethane (1:9) to give 510 mg of pure acetate.

The substituted 1,3-diol to prepare **31.17** was made by the following method.

Methyl carbonate formation of 2-(hydroxymethyl)-1,3-propanediol:

To a solution of 2-(hydroxymethyl)-1,3-propanediol (1 g, 9.4 mmol) in dichloromethane (20 mL) and pyridine (7.5 mL) at 0° C was added methyl chloroformate (0.79 mL, 9.4 mmol) slowly. The resulting solution was warmed to room temperature and stirred for 16 h. The reaction was concentrated under reduced pressure and chromatographed by eluting with methanol-dichloromethane (1:4) to give 650 mg of pure carbonate.

Example 32.

General procedure for 2-(3-phthalidyl)ethyl phosphonate diesters:

Followed the same procedure as in Example 18, Method B

The following compounds were prepared in this manner:

32.1: 4,5-Dimethyl-6-chloro-1-cyclopropylmethyl-2-[5-furanyl-2-bis-2-(3-phthalidylethyl)phosphonate]benzimidazole. Anal. Cald. for $C_{37}H_{34}N_2O_8PCl$ + 1.2 H_2O: C: 61.49; H: 5.08; N: 3.88; Found: C: 61.29; H: 4.89; N: 3.72

2-(3-phthalidyl)ethanol was prepared by the following method.

A solution of phthalide-3-acetic acid (1 mmol) in THF was treated with borane dimethylsulfide (1.5 mmol) at 0 °C for 1h, and 25 °C for 24 h. Extraction and chromatography gave 2-(3-phthalidyl)ethanol as a light yellow oil. TLC: R_f = 0.25, 50% EtOAc - hexane.

Example 33.

Preparation of benzimidazole phosphonate amine salts

A mixture of 1-cyclopropanemethyl-6-chloro-4,5-dimethyl-2-(2-(5-phosphono)furanyl)benzimidazole (1 mmol) and tris(hydroxymethyl)aminomethane (1.05 mmol) in methanol was stirred at 25 °C for 24 h. Evaporation of the solvent gave the salt as an yellow solid.

33.1: 1-cyclopropanemethyl-6-chloro-4,5-dimethyl-2-(2-(5-phosphono)furanyl)benzimidazole tris(hydroxymethyl)aminomethane. mp 175-178 °C; Anal. calcd. for $C_{21}H_{29}N_3O_7PCl + 2.3\ H_2O$: C: 46.42; H: 6.23; N: 7.73. Found: C: 46.16; H: 6.22; N: 7.98.

Examples of use of the method of the invention includes the following. It will be understood that these examples are exemplary and that the method of the invention is not limited solely to these examples.

For the purposes of clarity and brevity, chemical compounds are referred to by synthetic Example number in the biological examples below.

Besides the following Examples, assays that may be useful for identifying compounds which inhibit gluconeogenesis include the following animal models of diabetes:

i. Animals with pancreatic b-cells destroyed by specific chemical cytotoxins such as Alloxan or Streptozotocin (e.g. the Streptozotocin-treated mouse, -rat, dog, and -monkey). Kodama, H., Fujita, M., Yamaguchi, I., Japanese Journal of Pharmacology 66, 331-336 (1994) (mouse); Youn, J.H., Kim, J.K., Buchanan, T.A., Diabetes 43, 564-571 (1994) (rat); Le Marchand, Y., Loten, E.G., Assimacopoulos-Jannet, F., et al., Diabetes 27, 1182-88 (1978) (dog); and Pitkin, R.M., Reynolds, W.A., Diabetes 19, 70-85 (1970) (monkey).

ii. Mutant mice such as the C57BL/Ks db/db, C57BL/Ks ob/ob, and C57BL/6J ob/ob strains from Jackson Laboratory, Bar Harbor, and others such as Yellow Obese, T-KK, and New Zealand Obese. Coleman, D.L., Hummel, K.P., Diabetologia 3, 238-248 (1967) (C57BL/Ks db/db); Coleman, D.L., Diabetologia 14, 141-148 (1978) (C57BL/6J ob/ob); Wolff, G.L., Pitot, H.C.,

Genetics 73, 109-123 (1973) (Yellow Obese); Dulin, W.E., Wyse, B.M., Diabetologia 6, 317-323 (1970) (T-KK); and Bielschowsky, M., Bielschowsky, F. Proceedings of the University of Otago Medical School 31, 29-31 (1953) (New Zealand Obese).

iii. Mutant rats such as the Zucker fa/fa Rat rendered diabetic with Streptozotocin or Dexamethasone, the Zucker Diabetic Fatty Rat, and the Wistar Kyoto Fatty Rat. Stolz, K.J., Martin, R.J. Journal of Nutrition 112, 997-1002 (1982) (Streptozotocin); Ogawa, A., Johnson, J.H., Ohnbeda, M., McAllister, C.T., Inman, L., Alam, T., Unger, R.H., The Journal of Clinical Investigation 90, 497-504 (1992) (Dexamethasone); Clark, J.B., Palmer, C.J., Shaw, W.N., Proceedings of the Society for Experimental Biology and Medicine 173, 68-75 (1983) (Zucker Diabetic Fatty Rat); and Idida, H., Shino, A., Matsuo, T., et al., Diabetes 30, 1045-1050 (1981) (Wistar Kyoto Fatty Rat).

iv. Animals with spontaneous diabetes such as the Chinese Hamster, the Guinea Pig, the New Zealand White Rabbit, and non-human primates such as the Rhesus monkey and Squirrel monkey. Gerritsen, G.C., Connel, M.A., Blanks, M.C., Proceedings of the Nutrition Society 40, 237 245 (1981) (Chinese Hamster); Lang, C.M., Munger, B.L., Diabetes 25, 434-443 (1976) (Guinea Pig); Conaway, H.H., Brown, C.J., Sanders, L.L. eta l., Journal of Heredity 71, 179-186 (1980) (New Zealand White Rabbit); Hansen, B.C., Bodkin, M.L., Diabetologia 29, 713-719 (1986) (Rhesus monkey); and Davidson, I.W., Lang, C.M., Blackwell, W.L., Diabetes 16,395-401 (1967) (Squirrel monkey).

v. Animals with nutritionally induced diabetes such as the Sand Rat, the Spiny Mouse, the Mongolian Gerbil, and the Cohen Sucrose-Induced Diabetic Rat. Schmidt-Nielsen, K., Hainess, H.B., Hackel, D.B., Science 143, 689-690 (1964) (Sand Rat); Gonet, A.E., Stauffacher, W., Pictet, R., et al., Diabetologia 1, 162-171 (1965) (Spiny Mouse); Boquist, L., Diabetologia 8, 274-282 (1972) (Mongolian Gerbil); and Cohen, A.M., Teitebaum, A., Saliternik, R., Metabolism 21, 235-240 (1972) (Cohen Sucrose-Induced Diabetic Rat).

vi. Any other animal with one of the following or a combination of the following characteristics resulting from a genetic predisposition, genetic engineering, selective breeding, or chemical or nutritional induction: impaired glucose tolerance, insulin resistance, hyperglycemia, obesity, accelerated gluconeogenesis, increased hepatic glucose output.

BIOLOGICAL EXAMPLES

Example A: Inhibition of Human Liver FBPase

E. coli strain BL21 transformed with a human liver FBPase-encoding plasmid was obtained from Dr. M. R. El-Maghrabi at the State University of New York at Stony Brook. hlFBPase was typically purified from 10 liters of *E. coli* culture as described (M. Gidh-Jain et al. ,1994, *The Journal of Biological Chemistry* 269, pp 27732-27738). Enzymatic activity was measured spectrophotometrically in reactions that coupled the formation of product (fructose 6-phosphate) to the reduction of dimethylthiazoldiphenyltetrazolium bromide (MTT) via NADP and phenazine methosulfate (PMS) , using phosphoglucose isomerase and glucose 6-phosphate dehydrogenase as the coupling enzymes. Reaction mixtures (200 µl) were made up in 96-well microtitre plates, and consisted of 50 mM Tris-HCl, pH 7.4, 100 mM KCl, 5 mM EGTA, 2 mM MgCl2, 0.2 mM NADP, 1 mg/ml BSA, 1 mM MTT, 0.6 mM PMS, 1 unit/mL phosphoglucose isomerase, 2 units/mL glucose 6-phosphate dehydrogenase, and 0.150 mM substrate (fructose 1,6-bisphosphate). Inhibitor concentrations were varied from 0.01 µM to 10 µM. Reactions were started by the addition of 0.002 units of pure hlFBPase and were monitored for 7 minutes at 590 nm in a Molecular Devices Plate Reader (37°C).

Figure 2 shows the concentration-dependent inhibitory activity of compounds **12.61**, **12.53**, **12.52**, and **12.64**.

Table 2 below provides the IC_{50} values for several compounds prepared in Examples 12 and 13. The IC_{50} for AMP is 1.0µM.

Table 2

Example Compound Number	IC_{50} (human liver FBPase(µM)
12.6	6.5
12.37	4.2
12.35	1.2
13.5	4.7
12.52	2.5
12.54	0.1
12.57	3.8

13.21	2.5
12.61	0.06
13.25	1.8
12.64	0.06
13.52	10.5
13.56	0.78
13.61	0.1
13.66	4.0
12.80	0.035
12.82	0.04
12.79	0.08
15.1	0.18
12.84	0.055
13.96	0.16

Inhibitors of FBPase may also be identified by assaying rat and mouse liver FBPase.

Inhibition of rat liver and mouse liver FBPase

E. coli strain BL21 transformed with a rat liver FBPase-encoding plasmid was obtained from Dr. M. R. El-Maghrabi at the State University of New York at Stony Brook, and purified as described (El-Maghrabi, M.R., and Pilkis, S.J. (1991) Biochem. Biophys. Res. Commun. **176**: 137-144). Mouse liver FBPase was obtained by homogenizing freshly isolated mouse liver in 100 mM Tris-HCl buffer, pH 7.4, containing 1 mM EGTA, and 10% glycerol. The homogenate was clarified by centrifugation, and the 45-75% ammonium sulfate fraction prepared. This fraction was redissolved in the homogenization buffer and desalted on a PD-10 gel filtration column (Biorad) eluted with same. This partially purified fraction was used for enzyme assays. Both rat liver and mouse liver FBPase were assayed as described for human liver FBPase. Generally, as reflected by higher IC_{50} values, the rat and mouse liver enzymes are less sensitive to inhibition by the compounds tested than the human liver enzyme.

The following Table depicts the IC50 values for several compounds prepared in the Examples:

Compound	IC50 Rat Liver (µM)	IC50 Mouse Liver (µM)
12.6	>20	>20
12.37	>20	1.27
12.35	>20	>20
12.52	>20	0.78
12.54	>2	1.07
12.57	>20	>20
12.61	2.18	>20
12.64	0.55	1.07
13.21	>20	>20
13.25	>2	>20
13.56	>2	>20
13.61	>20	>20
13.66	>20	>20
12.80	0.15	0.3
12.82	0.2	0.3
12.79	0.45	0.72
15.1	1.0	1.5
12.84	0.4	0.5
13.96	1.95	0.7

Example B: AMP Site Binding

To determine whether compounds bind to the allosteric AMP binding site of hlFBPase, the enzyme was incubated with radiolabeled AMP in the presence of a range of test compound concentrations. The reaction mixtures consisted of 25 mM ^{3}H-AMP (54 mCi/mmol) and 0 -1000 mM test compound in 25 mM Tris-HCl, pH 7.4, 100 mM KCl and 1 mM $MgCl_2$. 1.45 mg of homogeneous FBPase (±1 nmole) was added last. After a 1 minute incubation, AMP bound to FBPase was separated from unbound AMP by means of a centrifugal ultrafiltration unit ("Ultrafree-MC", Millipore) used according to the instructions of the manufacturer. The radioactivity in aliquots (100 µL) of the upper compartment of the unit (the retentate, which contrains enzyme and label) and the lower compartment (the filtrate, which contains unbound label) were quantified using a Beckman liquid scintillation counter. The amount of AMP bound to the enzyme was estimated by comparing the counts in the filtrate (the unbound label) to the total counts in the retentate.

As evident from Fig. 3, both 5-aminoimidazole-4-carboxamide riboside monophosphate (ZMP) and compound **12.1** displaced AMP from hlFBPase in a dose-dependent manner, indicating that they bind to the same site on the

enzyme as AMP. As expected, compound **12.1** -a more potent hlFBPase inhibitor than ZMP (IC_{50}'s = 2 and 12 μM, respectively)- had a lower ED_{50} for AMP displacement than ZMP (50 vs 250 μM).

Example C: AMP Site/Enzyme Selectivity

To determine the selectivity of compounds towards FBPase, effects of FBPase inhibitors on 5 key AMP binding enzymes were measured using the assays described below:

Adenosine Kinase: Human adenosine kinase was purified from an *E. coli* expression system as described by Spychala *et al.* (Spychala, J., Datta, N.S., Takabayashi, K., Datta, M., Fox, I.H., Gribbin, T., and Mitchell, B.S. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 1232-1237). Activity was measured essentially as described by Yamada *et al.* (Yamada, Y., Goto, H., Ogasawara, N. (1988) *Biochim. Biophys. Acta* **660**, 36-43.) with a few minor modifications. Assay mixtures contained 50 mM TRIS-maleate buffer, pH 7.0, 0.1% BSA, 1 mM ATP 1 mM $MgCl_2$, 1.0 μM [U-^{14}C] adenosine (400-600 mCi/mmol) and varying duplicate concentrations of inhibitor. ^{14}C-AMP was separated from unreacted ^{14}C-adenosine by absorption to anion exchange paper (Whatman) and quantified by scintillation counting.

Adenosine Monophosphate Deaminase: Porcine heart AMPDA was purified essentially as described by Smiley *et al.* (Smiley, K.L., Jr, Berry, A.J., and Suelter, C.H. (1967) *J. Biol. Chem.* **242**, 2502-2506) through the phosphocellulose step. Inhibition of AMPDA activity was determined at 37° C in a 0.1 mL assay mixture containing inhibitor, ~0.005 U AMPDA, 0.1% bovine serum albumin, 10 mM ATP, 250 mM KCl, and 50 mM MOPS at pH 6.5. The concentration of the substrate AMP was varied from 0.125 - 10.0 mM. Catalysis was initiated by the addition of enzyme to the otherwise complete reaction mixture, and terminated after 5 minutes by injection into an HPLC system. Activities were determined from the amount of IMP formed during 5 minutes. IMP was separated from AMP by HPLC using a Beckman Ultrasil-SAX anion exchange column (4.6 mm x 25 cm) with an isocratic buffer system (12.5 mM potassium phosphate, 30 mM KCl, pH 3.5) and detected spectrophotometrically by absorbance at 254 nm.

Phosphofructokinase: Enzyme (rabbit liver) was purchased from Sigma. Activity was measured at 30° C in reactions in which the formation of fructose 1,6-bisphosphate was coupled to the oxidation of NADH via the action of aldolase, triosephosphate isomerase, and α-glycerophosphate dehydrogenase. Reaction mixtures (200 μL) were made up in 96-well microtitre plates and were read at 340 nm in a Molecular Devices Microplate Reader. The mixtures consisted of 200 mM Tris-HCl pH 7.0, 2 mM DTT, 2 mM $MgCl_2$, 0.2 mM NADH, 0.2 mM ATP, 0.5 mM Fructose 6-phosphate, 1 unit aldolase/ml, 3 units/ml triosephosphate isomerase, and 4 units/mL α-glycerophosphate dehydrogenase. Test compound concentrations ranged from 1 to 500 μM. Reactions were started by the addition of 0.0025 units of phosphofructokinase and were monitored for 15 minutes.

Glycogen Phosphorylase: Enzyme (rabbit muscle) was purchased from Sigma. Activity was measured at 37° C in reactions in which the formation of glucose 1-phosphate was coupled to the reduction of NADP via phosphoglucomutase and glucose 6-phosphate dehydrogenase. Assays were performed on 96-well microtitre plates and were read at 340 nm on a Molecular Devices Microplate Reader. Reaction mixtures consisted of 20 mM imidazole, pH 7.4, 20 mM $MgCl_2$, 150 mM potassium acetate, 5 mM potassium phosphate, 1 mM DTT, 1 mg/ml BSA, 0.1 mM NADP, 1 unit/mL phosphoglucomutase, 1 unit/mL glucose 6-phosphate dehydrogenase, 0.5 % glycogen. Test compound concentrations ranged from 1 to 500 μM. Reactions were started by the addition of 17 μg enzyme and were monitored for 20 minutes.

Adenylate Kinase: Enzyme (rabbit muscle) was purchase from Sigma. Activity was measured at 37° C in reaction mixtures (100 μL) containing 100 mM Hepes, pH 7.4, 45 mM $MgCl_2$, 1 mM EGTA, 100 mM KCl, 2 mg/ml BSA, 1 mM AMP and 2 mM ATP. Reactions were started by addition of 4.4 ng enzyme and terminated after 5 minutes by addition of 17 μL perchloric acid. Precipitated protein was removed by centrifugation and the supernatant neutralized by addition of 33 μL 3 M KOH/3 M KH_2CO3. The neutralized solution was clarified by centrifugation and filtration and analyzed for ADP content (enzyme activity) by HPLC using a YMC ODS AQ column (25 X 4.6 cm). A gradient was run from 0.1 M KH2PO4, pH 6, 8 mM tetrabutyl ammonium hydrogen sulfate to 75% acetonitrile. Absorbance was monitored at 254 nM.

Compound **12.1**, a 2 µM hlFBPase inhibitor, was essentially inactive in all of the above described assays except for the AMP deaminase screen: half-maximal inhibition of AMP deaminase was observed at a 42-fold higher concentration than the IC_{50} for FBPase. Compound **12.61** (hlFBPase IC_{50} = 0.055 µM) , in addition to being essentially without effect on adenosine kinase, adenylate kinase, glycogen phosphorylase, and phosphofructokinase, was almost 600-fold less potent on AMP deaminase. Compound **12.64** was tested in the glycogen phosphorylase assay only; no activation of the enzyme was observed at concentrations of drug ranging from 5 to 500 µM. The data suggest that compound **12.61** binds to hlFBPase in a highly selective manner. Table 3 below gives the selectivity data for compounds **12.61** and **12.64**.

Table 3
Selectivity

	Compound **12.1** (µM)	Compound **12.61**	Compound **12.64**
FBPase (inh.)	2.0	0.055	0.055
Adenosine Kinase (inh.)	>>10	>>100	
Adenylate Kinase (inh.)	>>500	>>500	
AMP Deaminase (inh.)	85	32	
Glycogen Phosphorylase (act.)	>>200	>>100	>>500
Phosphofructokinase (act.)	>>200	>>100	

Example D: Inhibition of Gluconeogenesis in Rat Hepatocytes

Hepatocytes were prepared from overnight fasted Sprague-Dawley rats (250-300 g) according to the procedure of Berry and Friend (Berry, M.N., Friend, D.S., 1969, J. Cell. Biol. 43, 506-520) as modified by Groen (Groen, A.K., Sips, H.J., Vervoorn, R.C., Tager, J.M. , 1982, Eur. J. Biochem. 122, 87-93). Hepatocytes (75 mg wet weight/mL) were incubated in 1 ml Krebs-bicarbonate buffer containing 10 mM Lactate, 1 mM pyruvate, 1 mg/mL BSA, and test

compound concentrations from 1 to 500 µM. Incubations were carried out in a 95% oxygen, 5% carbon dioxide atmosphere in closed, 50-mL Falcon tubes submerged in a rapidly shaking water bath (37° C). After 1 hour, an aliquot (0.25 mL) was removed, transferred to an Eppendorf tube and centrifuged. 50 µL of supernatant was then assayed for glucose content using a Sigma Glucose Oxidase kit as per the manufacturer's instructions.

Compounds **12.1**, **12.53**, and **12.61** inhibited glucose production from lactate/pyruvate in isolated rat hepatocytes in a dose-dependent manner, with IC_{50}'s of 110, 2.4 and 3.3 µM, respectively, as shown in Figure 4. IC_{50}'s for other select compounds in this assay are shown in the Table below. Compound **30.2** is a prodrug of compound **12.50.**

Compound	IC50 Glucose Production, µM
12.42	14
12.44	14
12.50	17
12.54	3.6
12.62	5
12.63	16
12.64	2.5
18.2	17
12.80	1.6
12.82	2.2
12.79	1.0
12.84	9
15.1	16

FBPase from rat liver is less sensitive to AMP than that from human liver. IC_{50} values are consequently higher in rat hepatocytes than would be expected in human hepatocytes.

Example E: Blood Glucose Lowering in Fasted Rats

Sprague Dawley rats (250-300 g) were fasted for 18 hours and then dosed intraperitoneally with 20 mg/kg of compounds **12.53**, **12.61**, or **12.64**. The vehicle used for drug administration was 50 mM sodium bicarbonate. Blood samples were obtained from the tail vein of conscious animals just prior to

injection and one hour post injection. Blood glucose was measured using a HemoCue Inc. glucose analyzer according to the instructions of the manufacturer.

Compound **12.53** lowered blood glucose by 55±14%, compound **12.61** by 48±15%, and compound **12.64** by 64.6±24%.

Example F: Effect of Compound 12.64 on gluconeogenesis from lactate/pyruvate in rat hepatocytes: glucose production inhibition and fructose 1,6-bisphosphate accumulation

Isolated rat hepatocytes were prepared as described in Example D and incubated under the identical conditions described. Reactions were terminated by removing an aliquot (250 µL) of cell suspension and spinning it through a layer of oil (0.8 mL silicone/mineral oil, 4/1) into a 10% perchloric acid layer (100 µL). After removal of the oil layer, the acidic cell extract layer was neutralized by addition of 1/3rd volume of 3 M KOH/3 M KH2CO3. After thorough mixing and centrifugation, the supernatant was analyzed for glucose content as described in Example D, and also for fructose 1,6-bisphosphate. Fructose 1,6-bisphosphate was assayed spectrophotometrically by coupling its enzymatic conversion to glycerol 3-phosphate to the oxidation of NADH, which was monitored at 340 nm. Reaction mixtures (1 mL consisted of 200 mM Tris-HCl, pH 7.4, 0.3 mM NADH, 2 units/mL glycerol 3-phsophate dehydrogenase, 2 units/ml triosephosphate isomerase, and 50-100 µL cell extract. After a 30 minute preincubation at 37°C, 1 unit/mL of aldolase was added and the change in absorbance measured until a stable value was obtained. 2 moles of NADH are oxidized in this reaction per mole of fructose 1,6-bisphosphate present in the cell extract.

As shown in Figure 5, compound **12.64** inhibited glucose production from lactate/pyruvate in rat hepatocytes (IC50 approx. 3 µM) The dose-dependent accumulation of fructose 1,6 bisphosphate (the substrate of FBPase) that occurred upon cell exposure to compound **12.64** is consistent with the inhibition of FBPase.

Example G: Analysis of Drug Levels And Liver Accumulation in Rats

Sprague-Dawley rats (250-300 g) were fasted for 18 hours and then dosed intraperitoneally either with saline (n = 3) or 20 mgs/kg of FBPase

inhibitor (n = 4). The vehicle used for drug administration was 10 mM bicarbonate. One hour post injection rats were anesthetized with halothane and a liver biopsy (approx. 1 g) was taken as well as a blood sample (2 ml) from the posterior vena cava. A heparin flushed syringe and needle was used for blood collection. The liver sample was immediately homogenized in ice-cold 10% perchloric acid (3 mL), centrifuged, and the supernatant neutralized with 1/3rd volume of 3 M KOH/3 M KH_2CO3. Following centrifugation and filtration, 50 µl of the neutralized extract was analyzed for FBPase inhibitor content by HPLC. A reverse phase YMC ODS AQ column (250 x 4.6 cm) was used and eluted with a gradient from 10 mM sodium phosphate pH 5.5 to 75% acetonitrile. Absorbance was monitored at 310 nm. (The concentration of fructose-1,6-bisphosphate in liver is also quantified using the method described in Example F. An elevation of fructose-1,6-bisphosphate levels in the livers from the drug-treated group is consistent with the inhibition of glucose production at the level of FBPase in the gluconeogenic pathway.) Blood glucose was measured in the blood sample as described in Example D. Plasma was then quickly prepared by centrifugation and extracted by addition of methanol to 60% (v/v). The methanolic extract was clarified by centrifugation and filtration and then analyzed by HPLC as described above.

Compound **12.64** achieved plasma acid liver levels of 85 µM and 90 nmoles/gram, respectively, one hour post injection of a 20 mg/kg dose.

Example H: Blood Glucose Lowering in Zucker Diabetic Fatty Rats

Zucker Diabetic Fatty rats purchased at 7 weeks of age are used at age 16 weeks in the 24-hour fasted state. The rats are purchased from Genetics Models Inc. and fed the recommended Purina 5008 diet (6.5% fat). Their fasting hyperglycemia at 24 hours generally ranges from 150 mg/dL to 310 mg/dL blood glucose.

FBPase inhibitor is administered at a dose of 50 mg/kg by intraperitoneal injection (n = 6). The stock solution is made up at 25 mg/mL in deionized water and adjusted to neutratility by dropwise addition of 5 N NaOH. 5 control animals are dosed with saline. Blood glucose is measured at the time of dosing and 2 hours post dose as described in Example D.

Example I: Inhibition of gluconeogenesis by FBPase inhibitor in Zucker Diabetic Fatty rats

Nine Zucker Diabetic Fatty rats (16-weeks old, Genetics Models Inc., Indianapolis, Indiana) were fasted at midnight and instrumented with jugular catheters the following morning. At noon, a dose of 50 mg/kg compound **12.64** (n = 3) or saline (n = 3) was administered as a bolus via the jugular catheter. After 50 minutes a bolus of ^{14}C-sodium bicarbonate (40 µCi/100 g body weight) was administered via the same route. 20 minutes later, the animals were quickly anesthetized with intravenous pentobarbitol and a blood sample (1.5 mL) was taken by cardiac puncture. Blood (0.5 mL) was diluted into 6 mL deionized water and protein precipitated by addition of 1 mL zinc sulfate (0.3 N) and 1 mL barium hydroxide (0.3 N). The mixture was centrifuged (20 minutes, 1000 x g) and 5 mL of the resulting supernatant was then combined with 1 g of a mixed bed ion exchange resin (1 part AG 50W-X8, 100-200 mesh, hydrogen form and 2 parts of AG 1-X8, 100-200 mesh, acetate form) to separate ^{14}C-bicarbonate from ^{14}C-glucose. The slurry was shaken at room temperature for four hours and then allowed to settle. An aliquot of the supernatant (0.5 mL) was then counted in 5 mL scintillation cocktail.

As indicated in the table below, compound **12.64** reduced the incorporation of ^{14}C-bicarbonate into ^{14}-C-glucose by approximately 50%.

Treatment	^{14}C-Glucose Produced (cpm/mL blood)	% Glucose Produced
Saline (n = 3)	66,651 ± 2365	100
12.64 (n = 3)	32,827 ± 6130	49.2

Example J: Blood Glucose Lowering in the Streptozotocin-treated Rat

Diabetes was induced in male Sprague-Dawley rats (250-300 g) by intraperitoneal injection of 55 mg/kg streptozotocin (Sigma Chemical Co.). Six days later, 24 animals were selected with fed blood glucose values (8 am) between 350 and 600 mg/dL and divided into two statistically equivalent groups. Blood glucose was measured in blood obtained from a tail vein nick by means of a HemoCue Inc. (Mission Viejo, CA) glucose analyzer. One group of 12 subsequently received compound **12.64** (100 mg/kg intraperitoneally) and

the other 12 ("controls") an equivalent volume of saline. Food was removed from the animals. Blood glucose was measured in each animal four hours after dosing, and a second dose of drug or saline was then administered. Four hours later, a final blood glucose measurement was made. As shown in the table below, compound **12.64** significantly reduced fasting blood glucose levels in the treated animal group, 8 hours after the initial dose:

	Blood glucose, mg/dl		p value
Treatment	T=0h	T=8h	(relative to controls)
Saline (n = 12)	489 ± 20	404 ± 19	
12.64 (n = 12)	488 ± 16	271 ± 29	0.001

Example K: Glucose lowering following oral administration of the Compound of Example 12.64

Compound **12.64** was administered by oral gavage at doses of 30, 100 and 250 mg/kg to 18-hour fasted, Sprague Dawley rats (250-300g; n= 4 - 5/group). The compound was prepared in deionized water, adjusted to neutrality with sodium hydroxide, and brought into solution by sonication prior to administration. Blood glucose was measured immediately prior to dosing, and at 1 hour intervals thereafter. Blood samples were obtained from the tail vein, and measurments made by means of a Hemocue glucose analyzer (Hemocue Inc, Mission Viejo, California) used according to the manufacturer's instructions. The 30 and 100 mg/kg doses were without effect, but profound hypoglycemia was elicited by the 250 mg/kg dose in 4 out of 5 animals dosed, within 1 hour of administration. The average glucose lowering in the four responding animals was 62 ± 8.6 % relative to saline-treated controls at the 1 hour time point.

Example L: Estimation of the oral bioavailability of prodrugs of phosphonic acids:

Prodrugs were dissolved in 10% ethanol/90% polyethylene glycol (mw 400) and administered by oral gavage at doses of approximately 20 or 40 mg/kg parent compound equivalents to 6-hour fasted, Sprague Dawley rats (220-240 g). The rats were subsequently placed in metabolic cages and urine was collected for 24 hours. The quantity of parent compound excreted into urine was determined by HPLC analysis. An ODS column eluted with a gradient from potassium phosphate buffer, pH 5.5 to acetonitrile was employed

for these measurements. Detection was at 310-325 nm. The percentage oral bioavailability was estimated by comparison of the recovery in urine of the parent compound generated from the prodrug, to that recovered in urine 24 hours after intravenous administration of unsubstituted parent compound at approximately 10 mg/kg. Parent compounds were typically dissolved in dimethyl sulfoxide, and administered via the tail vein in animals that were briefly anesthetized with halothane.

For Compound A, 6-amino-9-neopentyl, 8-(2-(5-diisobutyryloxymethylphosphono)furanyl purine, a prodrug of parent Compound B, 6-amino-9-neopentyl-8-(2-(5-phosphono)furanyl purine, 6.2% of an oral dose of approximately 20 mg/kg was recovered in urine. For the parent compound, 76.8% of an intravenous dose of approximately 10 mg/kg was recovered. The oral bioavailability of this prodrug was therefore calculated to be 6.2/76.8, or approximately 8%. The oral bioavailability of select other prodrugs are shown in the table below:

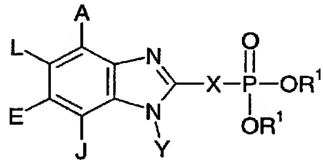
Prodrug (Example No.)	Parent compound (Example No.)	%Oral bioavailability
31.14	13.17	12.5
18.7	15.1	6.9
Compound C*	Compound B**	5.3
31.13	13.17	10.9
31.15	13.17	14.1

* Compound C is 6-amino-9-neopentyl-8-(2-(5-dipivaloyloxymethyl-phosphono)furanyl purine.

** Compound B is 6-amino-9-neopentyl-8-[2-(5-phosphono)]furanyl purine.

We claim:

1. The compounds of formula (I):



I

wherein:

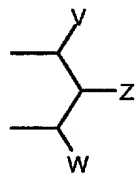
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, -CH(Ar)OH, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof; with the provisos that:

a) R^1 is not lower alkyl of 1-4 carbon atoms;

b) when X is alkyl or alkene, then A is $-N(R^8{}_2)$;

c) X is not alkylamine and alkylaminoalkyl substituted with phosphonic esters and acids; and

d) A, L, E, J, Y, and X together may only form 0-2 cyclic groups.

2. The compounds of claim 1 wherein when X is substituted with a phosphonic acid or ester, then A is $-N(R^8{}_2)$ and Y is not -H.

3. The compounds of claim 1 wherein X is not substituted with a phosphonic acid or ester.

4. The compounds of claim 1, with the additional proviso that when X is aryl or alkylaryl, said aryl or alkylaryl group is not linked 1,4 through a six-membered aromatic ring.

5. The compounds of claim 1 wherein A, L, and E are independently selected from the group consisting of -H, $-NR^8_2$, $-NO_2$, hydroxy, halogen, $-OR^7$, alkylaminocarbonyl, $-SR^7$, lower perhaloalkyl, and C1-C5 alkyl, or together E and J together form a cyclic group.

6. The compound of claim 5 wherein A, L and E are independently selected from the group consisting of $-NR^8_2$, -H, hydroxy, halogen, lower alkoxy, lower perhaloalkyl, and lower alkyl.

7. The compounds of claim 1 wherein A is selected from the group consisting of $-NR^8_2$, -H, halogen, lower perhaloalkyl, and lower alkyl.

8. The compounds of claim 1 wherein L and E are independently selected from the group consisting of -H, lower alkoxy, lower alkyl, and halogen.

9. The compounds of claim 1 wherein J is selected from the group consisting of -H, halogen, lower alkyl, lower hydroxyalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower perhaloalkyl, lower alkenyl, lower alkynyl, lower aryl, heterocyclic, and alicyclic, or together with Y forms a cyclic group.

10. The compounds of claim 9 wherein J is selected from the group consisting of -H, halogen, lower alkyl, lower hydroxyalkyl, $-NR^8_2$, lower R^8_2N-alkyl, lower haloalkyl, lower alkenyl, alicyclic, and aryl.

11. The compounds of claim 1 wherein Y is selected from the group consisting of -H, aralkyl, aryl, alicyclic, and alkyl, all except -H may be optionally substituted.

12. The compounds of claim 11 wherein Y is selected from the group consisting of alicyclic and lower alkyl.

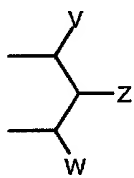
13. The compounds of claim 1 wherein X is selected from the group consisting of alkyl, alkynyl, alkoxyalkyl, alkylthio, aryl, alkylaminocarbonyl, alkylcarbonylamino, 1,1-dihaloalkyl, carbonylalkyl, alkyl(OH), and alkyl(sulfonate).

14. The compounds of claim 13 wherein X is selected from the group consisting of heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, alkyl(sulfonate), and alkoxyalkyl.

15. The compounds of claim 14 wherein X is selected from the group consisting of heteroaryl, alkylaminocarbonyl, and alkoxyalkyl.

16. The compounds of claim 15 wherein X is selected from the group consisting of methylaminocarbonyl, methoxymethyl and furanyl.

17. The compounds of claim 1 wherein each R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted phenyl, optionally substituted benzyl, optionally substituted alkylaryl, $-C(R^2)_2OC(O)R^3$, $C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2$-OC(O)SR^3, -alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxyl, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are alkyl-S-S-alkyl to form a cyclic group, or R^1 and R^1 together are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy,

alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

18. The compounds of claim 17 wherein each R^1 is independently selected from the group consisting of optionally substituted phenyl, optionally substituted benzyl, $-C(R^2)_2OC(O)R^3$, and -H.

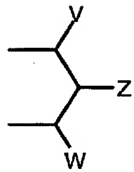
19. The compounds of claim 18 wherein R^1 is H.

20. The compounds of claim 17 wherein at least one R^1 is aryl, or $-C(R^2)_2$-aryl.

21. The compounds of claim 17 wherein at least one R^1 is $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-OC(O)OR^3$, $-C(R^2)_2-OC(O)SR^3$.

22. The compounds of claim 17 wherein at least one R^1 is alkyl-S-S-alkylhydroxyl, -alkyl-S-C(O)R^3, and -alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are alkyl-S-S-alkyl to form a cyclic group.

23. The compounds of claim 1 wherein together R^1 and R^1 are



wherein:

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic.

24. The compounds of claim 23 wherein V and W both form a 6-membered carbocyclic ring substituted with 0-4 groups, selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, and alkoxy; and Z is $-R^2$.

25. The method of claim 23 wherein V and W are hydrogen; and Z is selected from the group consisting of hydroxyalkyl, acyloxyalkyl, alkyloxyalkyl, and alkoxycarboxyalkyl.

26. The method of claim 23 wherein V and W are independently selected from the group consisting of hydrogen, optionally substituted aryl, and optionally substituted heteroaryl, with the proviso that at least one of V and W is optionally substituted aryl or optionally substituted heteroaryl.

27. The compounds of claim 1 wherein together R^1 and R^1 are optionally substituted lactones attached at the omega position.

28. The compounds of claim 17 wherein R^1 is alicyclic where the cyclic moiety contains carbonate or thiocarbonate.

29. The compounds of claim 28 wherein together R^1 and R^1 are optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen.

30. The compounds of claim 1 wherein

A, L and E are independently selected from the group consisting of $-NR^8_2$, -H, hydroxy, halogen, lower alkoxy, lower alkyl, and lower perhaloalkyl;

X is selected from the group consisting of aryl, alkoxyalkyl, alkyl, alkylthio, 1,1-dihaloalkyl, carbonylalkyl, alkyl(hydroxy), alkyl(sulfonate), alkylaminocarbonyl, and alkylcarbonylamino;

and each R^4 and R^7 is independently selected from the group consisting of -H and lower alkyl.

31. The compounds of claim 30 wherein A, L, and E are independently selected from the group consisting of -H, lower alkyl, halogen, and $-NR^8_2$;

J is selected from the group consisting of -H, halogen, haloalkyl, hydroxyalkyl, $-R^8_2$N-alkyl, lower alkyl, lower aryl, heterocyclic and alicyclic, or together with Y forms a cyclic group; and

X is selected from the group consisting of heteroaryl, alkylaminocarbonyl, 1,1-dihaloalkyl, and alkoxyalkyl.

32. The compounds of claim 31 wherein A is selected from the group consisting of -H, $-NH_2$, -F, and $-CH_3$;

L is selected from the group consisting of -H, -F, $-OCH_3$, Cl and $-CH_3$;

E is selected from the group consisting of -H, and -Cl;

J is selected from the group consisting of -H, halo, C1-C5 hydroxyalkyl, C1-C5 haloalkyl, C1-C5 $R^8{}_2$ N-alkyl, C1-C5 alicyclic, and C1-C5 alkyl;

X is $-CH_2OCH_2-$, 2,5-furanyl; and

Y is lower alkyl.

33. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -H, Y is isobutyl, and X is 2,5-furanyl.

34. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -Cl, Y is isobutyl, and X is 2,5-furanyl.

35. The compounds of claim 32 where A is -H, L is -H, E is -Cl, J is -H, Y is isobutyl, and X is 2,5-furanyl.

36. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -H, Y is cyclopropylmethyl, and X is 2,5-furanyl.

37. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is ethyl, Y is isobutyl, and X is 2,5-furanyl.

38. The compounds of claim 32 where A is $-CH_3$, L is -Cl, E is -H, J is -H, Y is isobutyl, and X is 2,5-furanyl.

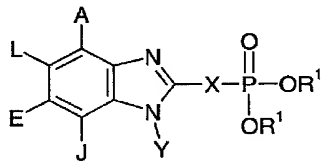
39. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is -Br, Y is isobutyl, and X is $-CH_2OCH_2$.

40. The compounds of claim 32 where A is $-NH_2$, L is -F, E is -H, J is selected from the group consisting of bromopropyl, bromobutyl, chlorobutyl, cyclopropyl, hydroxypropyl, N,N-dimethylaminopropyl, and X is 2,5-furanyl.

41. The compound of claim 32 wherein A is $-CH_3$, L is $-CH_3$, E is $-CH_3$, J is $-CH_3$, Y is cyclopropylmethyl, and X is 2,5-furanyl.

42. The compounds of claims 33, 34, 35, 36, 37, 38, 39, 40, or 41 wherein R^1 is pivaloyloxymethyl or their HCl salts.

43. A method of treating an animal for diabetes mellitus, comprising administering to said animal a therapeutically effective amount of a compound of formula 1:



wherein:

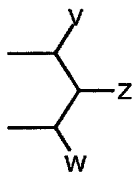
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are


,

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

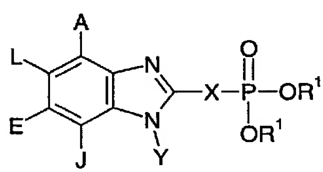
R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

44. A method of lowering blood glucose levels in an animal in need thereof, comprising administering to said animal a pharmaceutically acceptable amount of a compound of formula 1:



wherein:

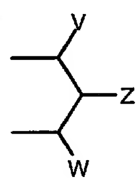
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R^9; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is -R^2, then at least one of V and W is not -H or -R^9;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

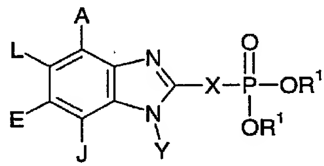
R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

45. A method of inhibiting FBPase at the AMP site in patients in need thereof, comprising administering to said patients an FBPase inhibitory amount of a compound of formula 1:



wherein:

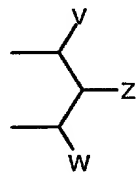
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

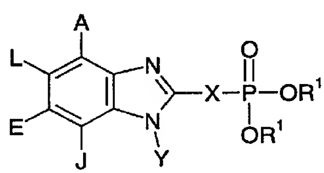
R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

46. A method of inhibiting gluconeogenesis in animal in need thereof, comprising administering to said animal an effective amount of a compound of formula 1:



wherein:

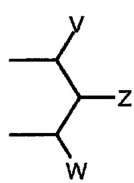
A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



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wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

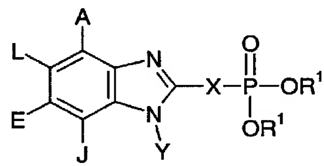
R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

47. A method of treating an animal for a disease derived from abnormally elevated insulin levels, comprising administering to said animal a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor which binds to the AMP site of FBPase.

48. The method of claim 47 wherein said inhibitor is a compound of formula 1:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

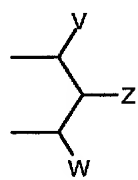
J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl,

alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, alkyl-S-$C(O)R^3$, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



,

wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2{}_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

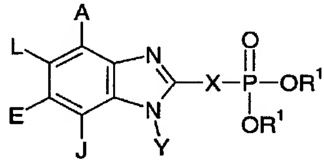
R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

49. The method of claim 47 wherein said disease is atherosclerosis.

50. A method of treating an animal with excess glycogen storage disease, comprising administering to said animal in need thereof a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor which binds to the AMP site of FBPase.

51. The method of claim 50 wherein said inhibitor is a compound of formula 1:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

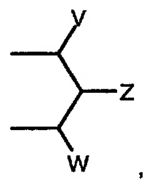
J is selected from the group consisting of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-dihaloalkyl, aminocarbonylamino, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with Y form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

Y is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted; or together with X form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, alkylaryl, $-C(R^2)_2OC(O)NR^2_2$,

-NR^2-C(O)-R^3, -$C(R^2)_2$- OC(O)R^3, $C(R^2)_2$-O-C(O)OR^3, -$C(R^2)_2$OC(O)SR^3, alkyl-S-C(O)R^3, alkyl-S-S-alkylhydroxy, and alkyl-S-S-S-alkylhydroxy, or together R^1 and R^1 are -alkyl-S-S-alkyl to form a cyclic group, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R^9; or

together V and Z are connected to form a cyclic group containing 3-5 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected to form a cyclic group containing 3 carbon atoms substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, and aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH_2OH, -CH_2OCOR^3, -CH_2OC(O)SR^3, -CH_2OCO_2R^3, -SR^3, -S(O)R^3, -CH_2N_3, -$CH_2NR^2_2$, -CH_2Ar, -CH(Ar)OH, -CH(CH=CR^2R^2)OH, -CH(C≡CR^2)OH, and -R^2;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is -R^2, then at least one of V and W is not -H or -R^9;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^9 is selected from the group consisting of alkyl, aralkyl, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

52. The methods of claims 43, 44, 45, 46, 47, 48, 49, 50, or 51 wherein said compounds are administered orally.

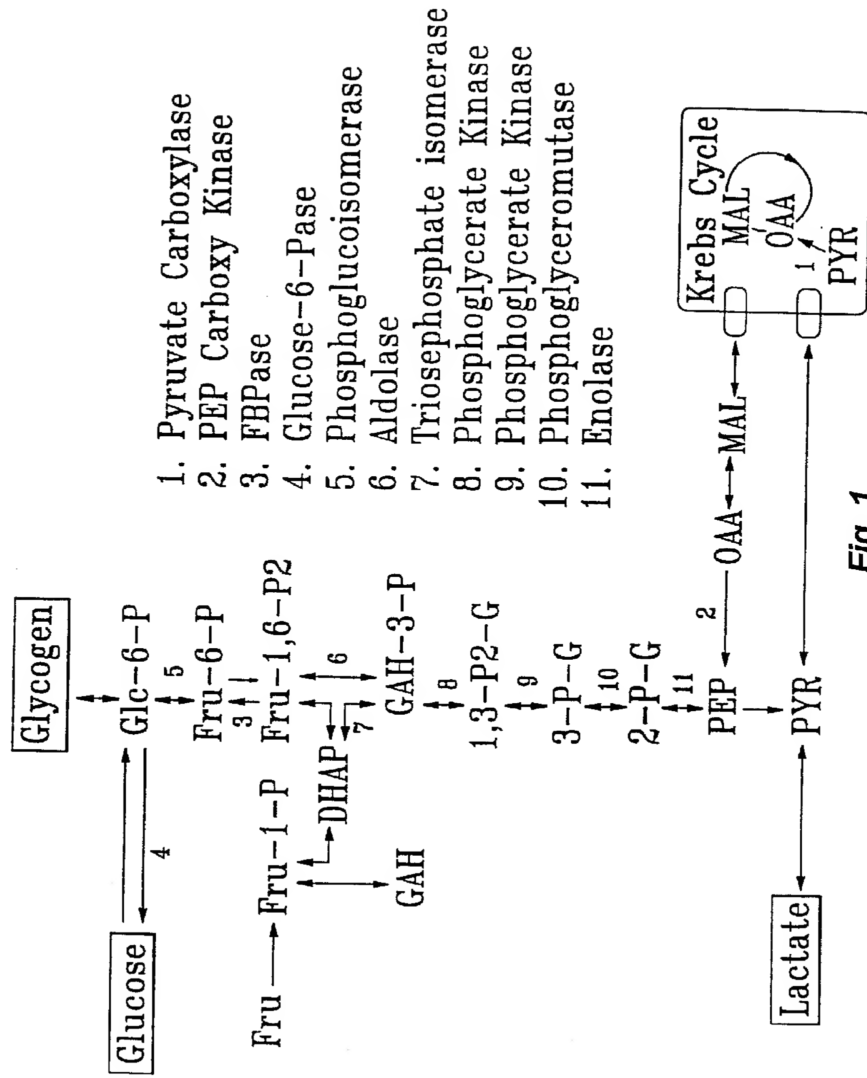

Glycogen
Glucose
Glc-6-P
Fru-6-P
Fru-1,6-P2
Fru
Fru-1-P
DHAP
GAH
GAH-3-P
1,3-P2-G
3-P-G
2-P-G
PEP
PYR
Lactate
OAA
MAL
Krebs Cycle
MAL
OAA
PYR
1. Pyruvate Carboxylase
2. PEP Carboxy Kinase
3. FBPase
4. Glucose-6-Pase
5. Phosphoglucoisomerase
6. Aldolase
7. Triosephosphate isomerase
8. Phosphoglycerate Kinase
9. Phosphoglycerate Kinase
10. Phosphoglyceromutase
11. Enolase

Fig. 1

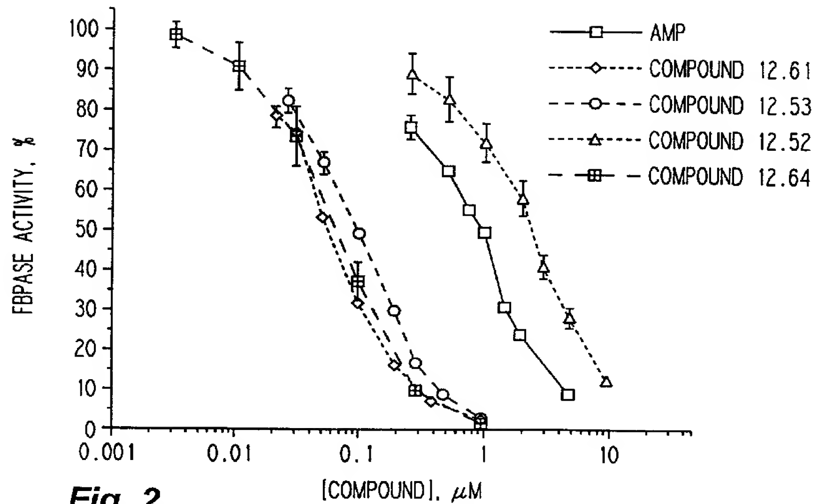

100
90
80
70
60
50
40
30
20
10
0
FBPASE ACTIVITY, %
0.001
0.01
0.1
1
10
[COMPOUND], μM
AMP
COMPOUND 12.61
COMPOUND 12.53
COMPOUND 12.52
COMPOUND 12.64

Fig. 2

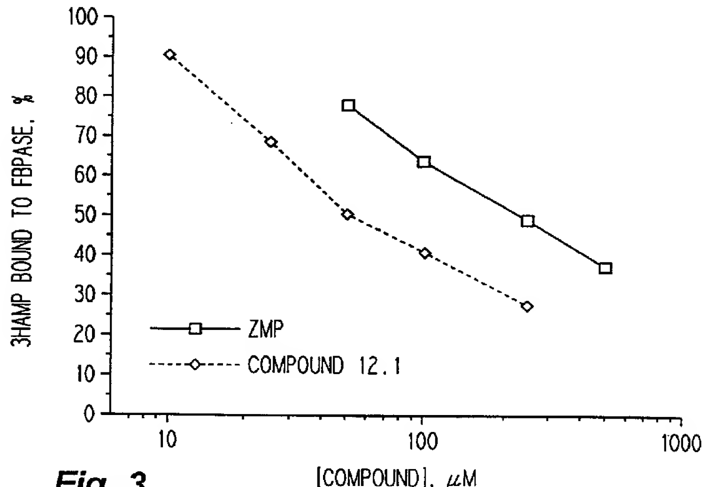

100
90
80
70
60
50
40
30
20
10
0
3HAMP BOUND TO FBPASE, %
10
100
1000
[COMPOUND], μM
ZMP
COMPOUND 12.1

Fig. 3

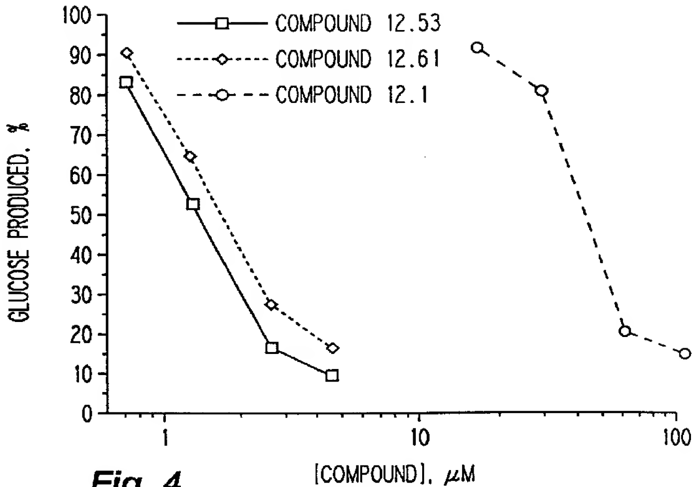

COMPOUND 12.53
COMPOUND 12.61
COMPOUND 12.1
GLUCOSE PRODUCED, %
100
90
80
70
60
50
40
30
20
10
0
1
10
100
[COMPOUND], μM

Fig. 4

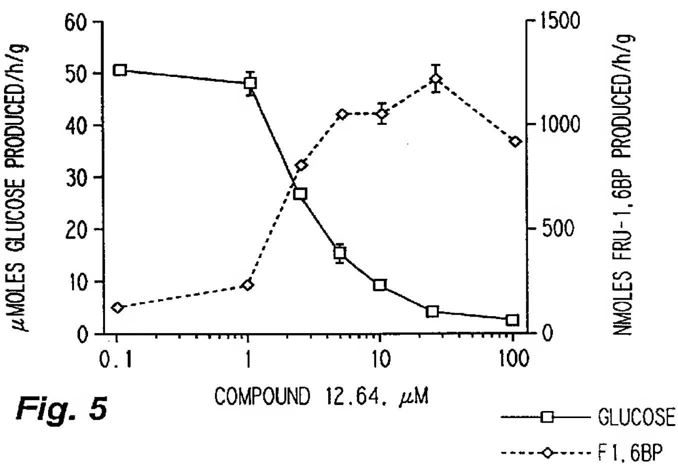

μMOLES GLUCOSE PRODUCED/h/g
NMOLES FRU-1,6BP PRODUCED/h/g
60
50
40
30
20
10
0
1500
1000
500
0
0.1
1
10
100
COMPOUND 12.64, μM
GLUCOSE
F1,6BP

Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No
PC'. .S 98/04498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07F9/6506 A61K31/675 C07F9/6558

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 427 799 B (GENSIA PHARMACEUTICALS, INC.) 30 November 1994 cited in the application see the whole document ---	1-52
Y	EP 0 354 322 A (AMERICAN CYANAMID CO.) 14 February 1990 see the whole document ---	1-52
Y	WO 94 07867 A (PFIZER INC.) 14 April 1994 see the whole document ---	1-52

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1998	26 Jun 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOHICHIRO YOSHINO: "Organic phosphorus compounds.2. Synthesis and coronary vasodilatator activity of (Benzothiazolylbenzyl)phosphonate derivatives." JOURNAL OF MEDICINAL CHEMISTRY., vol. 32, no. 7, - July 1989 WASHINGTON US, pages 1528-1532, XP002066780 cited in the application see the whole document	1-52
Y	EP 0 620 227 A (HOECHST JAPAN LTD.) 19 October 1994 cited in the application see the whole document	1-52
Y	WO 94 20508 A (EISAI CO. LTD.) 15 September 1994 see page 242, examples 305 and 306; claims	1-52
Y	EP 0 604 657 A (OTSUKA PHARMACEUTICAL FACTORY, INC.) 6 July 1994 see page 4, lines 8-14; page 11, table 1; page 16, examples 24-26	1-52
Y	US 5 021 443 A (NICOLE BRU-MAGNIEZ) 4 June 1991 see column 9 and claims	1-52
A	EP 0 012 909 A (BAYER AG) 9 July 1980 cited in the application see claim 1	1-42

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/04498

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 43 - 52
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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